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TYPES OF ORTHOSTATIC HYPOTENSION AND THEIR TREATMENT.

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With changes in posture, alterations in the hydrostatic factor of the blood pressure in different parts of the vascular bed tend to produce a redistribution of the bloodflow. This would impair the circulation of vital organs such as the brain and heart, were it not for the operation of certain well known reflexes. These reflexes are called into action whenever there is a sufficient change in blood pressure in the region of receptor mechanisms located in specific areas such as the carotid sinus, the aortic arch, the mesentery and probably in other areas. The subject has been reviewed by Bronk.[3]

When a normal person assumes the erect position, the hydrostatic fall in blood pressure stimulates these receptor endings. Peripheral vasoconstriction occurs suddenly as the vasomotor center responds to these afferent impulses. This adaptation is so prompt that the blood pressure usually appears to be well maintained at a level similar to that observed while reclining.

In orthostatic or postural hypotension there is a considerable fall in blood pressure upon standing, often accompanied by manifesta-

tions which are presumably the result of cerebral anemia. The clear description of such a syndrome by Bradbury and Eggleston[1] has stimulated an interest in the subject. Ellis and Haynes[8] have emphasized the frequent association of orthostatic hypotension with disease of the nervous system, and have investigated certain aspects of the abnormal physiology underlying the condition. Our report is an attempt to classify patients with orthostatic hypotension upon the basis of their reactions to tests of vasomotor function. A rationale of treatment is presented, based upon the defects believed to be important.

The effector mechanisms by which vasomotor reflexes exercise their control upon the cardiovascular system are of two types: First, reflex changes in the tone of peripheral vessels, under control of the sympathetic nerves, may alter the peripheral resistance of portions of the vascular bed. Secondly, reflex changes in the heart rate or volume ejected per beat may alter the cardiac output to meet the new situation. The relative importance of these two mechanisms has recently been studied in dogs.[9] It was of interest to investigate these two types of vasomotor activity when elicited by a change of posture from lying to standing, both in normal subjects and in patients with orthostatic hypotension.

Methods. It was difficult to obtain a measure of the early adaptive changes which may take place in the heart. Variations in pulse rate may reflect these to a certain extent. The pulse rate was measured from the plethysmographic records to be described, or by palpation at the wrist. As an index of peripheral vasomotor effects, changes in the bloodflow through a finger were measured. Finger bloodflow has been shown to provide a sensitive index of peripheral sympathetic activity.[4a] The peripheral sympathetic system tends characteristically to show mass activity, producing simultaneous changes in the blood vessels of the skin in widely different parts of the body. Therefore deductions made from changes of flow in a finger are by no means limited to the behavior of that digit.

Measurements of flow were made by the plethysmographic technique of Burton.[4a] The pulsations from a finger plethysmograph are recorded optically, utilizing a small rubber cuff placed above the plethysmograph for intermittent occlusion of the veins. Blood pressure was estimated on the opposite arm by the use of a Riva-Rocci cuff and auscultation. The subjects lay on a bed for 10 minutes, or until blood pressures were constant, after which a series of 20 or 30 determinations of blood flow were made. They then arose to stand quietly beside the bed, with the hand supported at the level of the heart. Measurements of flow and of blood pressure were then resumed immediately. Other methods occasionally employed in this study will be referred to subsequently.

Measurements of cardiac output[12] and of skin temperature,[15] before and after assuming the erect position, have been recorded by others. It must be emphasized, however, that these measurements cannot be made quickly enough to reflect the prompt adjustments which result from reflex activity.[4b] We have employed a standard test[10] of the capacity of the patient to develop vasodilatation when heat is applied to a distant extremity (to be referred to subsequently as *thermal reflex dilatation*), to serve merely as an indication of the integrity of the sympathetic nerves supplying the region tested.

I. *Normal Subjects.* Results for 6 normal subjects are shown in Figure 1. Here the mean pressure, computed as the mean of systolic and diastolic pressures, changed less than 8% between lying and standing. At the top of Chart 1 are shown single curves of flow, one just before, the other just after standing. From these are derived the changes in finger volume-pulsation, in flow (given by the initial slope of the rising curves), and in heart rate. The data shown graphically below these curves are from averages of many flow determinations for the 2 minutes immediately following the assumption of the standing position. The changes are plotted as percentages of the values obtained when lying.

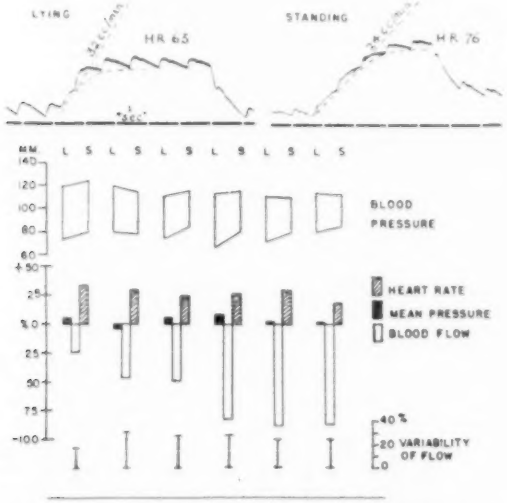

CHART 1.—Vasomotor reactions to standing in 5 normal subjects. At the top are shown samples of photographic records giving curves of bloodflow in a finger.

While there is considerable variation from one normal subject to another, there are features of the vasomotor response which were seen to be common to all. The pulse pressure usually diminished, associated with a rise in diastolic pressure and sometimes with a fall in systolic pressure. The heart rate increased by from 20 to 35%. In each case the finger bloodflow decreased markedly, in some cases by more than 80%. This decrease, by comparison with the slight changes in mean blood pressure, must indicate active constriction of the peripheral vessels. Measurements of skin temperature upon tilting a normal subject tend to confirm such vasoconstriction.[15] Thus, in all of our normal subjects there was evidence of both peripheral and cardiac reflex effects, but the relative importance of the two varied greatly in different individuals. Considerable variation might also be expected in the same individual under different

environmental conditions. If, for example, the peripheral vessels were already constricted by cold, when the subject changed his position from lying to standing it might be expected that the major burden of reflex change would be borne by the cardiac mechanism, as indicated by tachycardia. It is apparent, therefore, that evidence concerning the two types of reflex activity, peripheral and cardiac, must be considered in relation to their additive effects. There is the suggestion, in Chart 1, that when tachycardia is less marked, peripheral vasoconstriction is greater, and *vice versa*.

After several minutes of standing, other adaptive mechanisms must assume importance in the task of maintaining distribution of the blood, for the heart rate tends to decrease and the finger flow to increase. Tissue pressure, as it influences venous return, is probably a larger factor.[14] It is the inadequacy of these more slowly operating mechanisms that leads to syncope seen in "normal" subjects after several minutes of very quiet standing, or lying on a tilted table. In one subject we observed the initial reflex effects, but syncope intervened abruptly after a minute of standing. The abnormalities occurring with syncope of this type are probably different from those concerned in orthostatic hypotension as discussed in this paper.

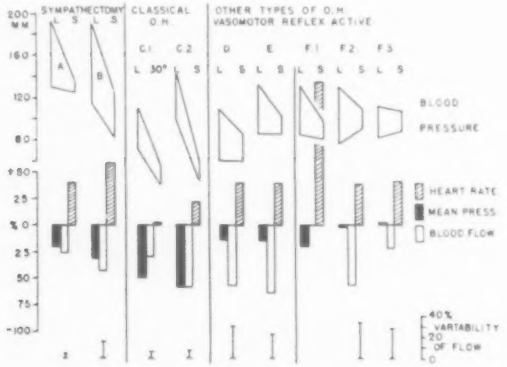

CHART 2.—Vasomotor reactions to standing, in 6 patients with orthostatic hypotension. Note absence of tachycardia in C–1 and C–2.

II. *Effects of Surgical Sympathectomy.* The important part played by the cardiovascular sympathetic reflexes was demonstrated by applying the same tests in cases where parts of the pathways had been interrupted. Chart 2*A* and 2*B* illustrate the reactions of 2 patients who had been subjected to surgical sympathectomy for arterial hypertension:

Patient A had just recovered from bilateral splanchnicectomy and lumbar ganglionectomy. In addition, paravertebral injections of absolute alcohol had been made by Dr. N. E. Freeman in an

attempt to interrupt the upper five thoracic rami communicantes. The decrease in finger bloodflow upon standing was not appreciably greater than would passively result from the considerable fall in blood pressure. Although the increase in heart rate was marked (accelerator mechanism not abolished by paravertebral injections), without the peripheral vasoconstriction there was a considerable fall in blood pressure.

Patient B gave evidence of cerebral damage resulting from a stroke. Following bilateral splanchnicectomy and lumbar ganglionectomy the slight decrease in finger bloodflow did not indicate active vasoconstriction in the finger. The fall in mean pressure, and increase in heart rate were even greater than shown by Patient A.

III. *Marked Impairment of Reflex Vasomotor Function—Organic Disease.* Orthostatic hypotension: Classical case.

W.L., a white man aged 45, began in 1934 to suffer from weakness, lassitude, dizziness, and attacks of unconsciousness sometimes accompanied by convulsions. These attacks were precipitated by exertion, occurred almost invariably while he was standing, and were aggravated by hot weather. They were originally considered to be idiopathic epilepsy.

In 1938 it was found that he had orthostatic hypotension.*

The patient gave no history of head injury or of syphilis or other infection. Prior to 1936 he had used both alcohol and tobacco to considerable excess. Further symptoms included loss of sexual desire and potency since 1933; intolerance to hot weather; failure to sweat save over a small area of the trunk; constipation, and pyrosis. Weakness was most marked upon arising in the mornings. No therapy had been found to give him relief.

Upon physical examination he was found to be of sthenic habitus. His complexion was usually ruddy, in contrast with the pallor said to be frequently associated with this disorder. When standing he would shuffle his feet constantly, unless he were specifically directed to the contrary. His blood pressure while lying varied from 120/70 to 150/110, his pulse from 65 to 90. Upon standing, his pulse did not accelerate, or increased by 20 beats per minute at most. The blood pressure usually fell to a level of 60/50 or lower after 1 or 2 minutes of quiet standing. The general examination was otherwise negative, save for the presence of small genitalia, and feminine distribution of pubic hair.

A neurologic examination performed April 19, 1940, by Dr. James S. Dean, revealed sluggish reactions of the pupils to light; abnormalities of associated movement and dysdiadokokinesis in the upper extremities; a disproportionate hyperreflexia in the lower extremities, with absence of normal plantar flexion and questionably positive Babinski's and Chaddock's signs on the left. These findings were interpreted to be "compatible with the presence of a considerable degree of bilateral cerebral atrophy."

An encephalogram, performed October 30, 1936, in the Temple University Hospital, was interpreted as indicating "a communicating hydrocephalus, apparently the result of arachnoid adhesions."

Repeated blood counts, urinalyses, and blood Wassermann reactions were not abnormal save for the finding of hyaline casts in a single urine specimen. Blood analyses gave the following results: blood urea nitrogen 11 mg. per 100 cc.; fasting blood sugar 76 mg. per 100 cc.; serum cholesterol

* We are indebted to Dr. John A. Reisinger, the Veterans' Administration, Washington, D. C., for this discovery, for referring the patient to us, and for allowing us to cite extensive investigations performed under his direction.

201 mg. per 100 cc.; serum proteins 6.3%; serum potassium 6.1 and calcium 11.6 milli-equivalents per liter. A glucose tolerance curve was normal. Analyses of gastric contents showed no free hydrochloric acid, and a maximum total acidity of 17 units.

The basal metabolic rate was −19% and −17% on two occasions. Repeated electrocardiograms showed left axis deviation, small *T* waves in Leads I and II, and inversion of *T* waves in Leads CF-4 and CF-5. Orthodiagrams were normal. Upon lumbar puncture no abnormalities of pressure, mechanics, chemistry or cytology were found.

During a period of observation in the University of Pennsylvania Hospital, on the service of Dr. O. H. P. Pepper, it was observed that his oral temperatures reflected that of his environment during warm weather (Chart 3). In addition, although he did not sweat spontaneously, even in a very warm room, the integrity of his sweat glands was evidenced by profuse generalized sweating after the subcutaneous injection of 10 mg. of acetyl-B-methylcholine, or 0.5 mg. of carbaminoylcholine chloride. The volume of urine secreted during the night was found to be slightly in excess of that passed during the day.

Further examinations bearing upon the abnormal physiology in this patient will be described later. A review of the literature indicates that not more than 12 cases of classical orthostatic hypotension are on record.

Chart 2, C-1 and C-2, illustrates the slight vasomotor activity shown by this patient. C-1 was obtained shortly after admission to this hospital. Since upon standing the patient was prone to lose consciousness, the test was performed by tilting his bed to an angle of 30°. Even with the very great fall in blood pressure, the increase in heart rate was insignificant, and the finger flow decreased relatively less than the mean pressure. Some months later, after treatment, the level of blood pressure while lying was higher, and the test could be made from lying to standing without fainting. Again, C-2, the diminution in finger bloodflow was not sufficiently great to indicate active vasoconstriction in spite of the marked fall in blood pressure. Nor did the degree of tachycardia correspond with the change in blood pressure.

Upon pressure over the carotid sinuses there was no change in heart rate, and the fall in systolic pressure was 10 mm. Hg. When nitroglycerin gr. 1/100 was given sublingually with the patient lying quietly, the change in heart rate was slight, the fall in blood pressure, marked: before, blood pressure 140/110, pulse 60; 10 minutes after, blood pressure 55/50 (?), pulse 78. From these tests we conclude that in this patient with classical orthostatic hypotension the vasomotor reflexes, both peripheral and cardiac, were markedly impaired.

The defects of his reflex vasomotor activity could be demonstrated in other ways: the flow of blood through the finger of a normal subject continually fluctuates between high and low values as a result of intermittent spontaneous activity of the sympathetic nervous system. Successive determinations of flow show a wide fluctuation (Chart 4-A). A measure of the degree of fluctuation is provided by the standard deviation from the mean of a series of 30 successive measurements.[5] Results for this are plotted as in Charts 1 and 2. The variability amounts to between ±20% and ±35% of the mean in normal subjects. In our patient, however, the flow was remarkably constant (Chart 4-B), the standard deviation being less than 7%. In all other types examined, the variability was normal, save in the patient illustrated in Chart 2-A, who gave evidence of cerebral damage following a stroke.

Any startling stimulus, such as the prick of a pin, will elicit in the normal an intense vasoconstriction of the finger vessels (Chart 5-A). In our case of classical orthostatic hypotension this reaction was absent (Chart 5-B).

The rhythmic fluctuations of peripheral flow seen in normal persons are related to the temperature regulatory functions.[5] It was not surprising, then, to find that our patient's regulation of body temperature was markedly deficient (Chart 3).

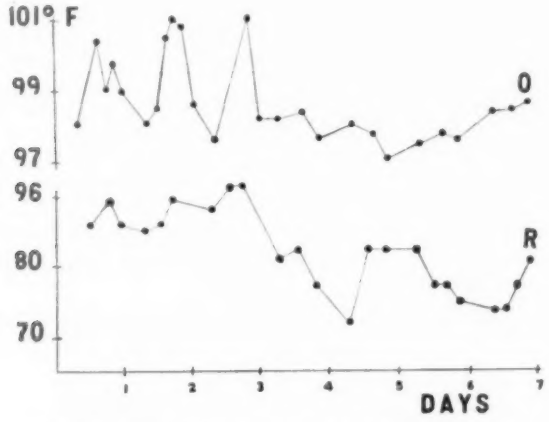

CHART 3.—Oral temperatures—*O*, of a patient with classical orthostatic hypotension, with corresponding room temperatures—*R*.

Upon heating W.L.'s legs and right hand, his left hand showed normal thermal reflex dilatation. No evidence of vasodilatation could be produced in either foot by this means, or by novocain block. We have no explanation for this discrepancy between the reactions of the upper and the lower extremities.

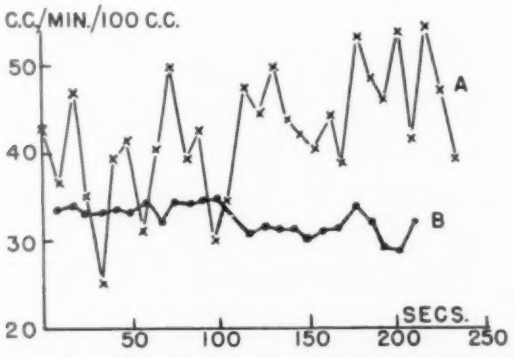

CHART 4.—Fluctuations of finger bloodflow in a normal person—*A*, and in a patient with classical orthostatic hypotension—*B*.

Central Location of Patient's Lesion: The lack of normal vasomotor activity, both spontaneous and reflex, in classical orthostatic hypotension, might be due to widespread lesions of the peripheral sympathetic nerves, or to a lesion located centrally. Evidence, in addition to the encephalogram, suggested that the lesion was central

rather than peripheral: The psychogalvanic response to a startling stimulus is indicative of reflex activity of the sweat glands.[6] Although W. L. showed no diminution of bloodflow, he gave a normal psychogalvanic response upon receiving such a stimulus. Anatomically, the sympathetic nerves supplying both the sweat glands and the blood-vessels lie together peripherally. The peripheral sympathetic nerves were therefore able to function. The absence of reflex vasomotor activity thus suggests that there was damage in or about the bulbar vasomotor centers.

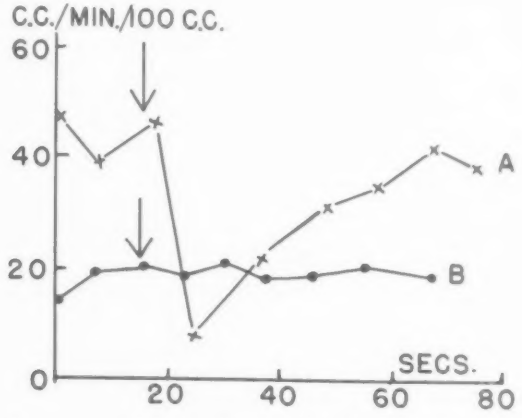

CHART 5.—Reflex vasoconstriction in the finger to a startling noise at the time marked by an arrow. *A*—normal subject. *B*—classical orthostatic hypotension.

IV. *Slight Impairment of Reflex Vasomotor Function. A.* Both Cardiac and Peripheral Mechanisms Involved: The tests which we have employed serve to distinguish the classical type of orthostatic hypotension from other cases in which there is a significant fall in blood pressure upon standing:

J.K. was a boy of 14 who had been afebrile for 9 days following lobar pneumonia, due to pneumococcus Type I, treated with sulfathiazole and type-specific serum. He was tested in the hope that he might show the fall in blood pressure upon standing which is reported to be a frequent accompaniment of convalescence from acute infectious diseases. This hope seemed amply justified, as illustrated in Chart 2-D. Despite considerable tachycardia and active vasoconstriction, there was a marked fall in blood pressure. Normal vasodilatation occurred in the toes following the application of heat to the arms, indicating no gross abnormality of the sympathetic nerves.

J.M., a young man of 18, suffered from attacks of unconsciousness with convulsions. Examinations of blood chemistry, cardiovascular structure and function, and of the central and peripheral nervous systems, revealed no obvious cause. A tentative diagnosis of idiopathic epilepsy was made. The basal metabolic rate was −32 and −38% in 1938, and −14 and −19% in 1940. His responses of blood pressure and heart rate upon standing were found to be normal in August, 1938. In June, 1940, the day following an

attack of unconsciousness and generalized convulsions, the blood pressure and pulse were discovered to be 100/70 and 60 while lying, but upon standing quietly for 2 minutes the blood pressure fell to 70/60 and the pulse rate increased to 144. The patient became pale, sweated profusely, and had to lie down because of faintness. Upon lying quietly he immediately felt better. His pulse rate and blood pressure returned to their resting values after one minute.

He was able to recall that 4 of his 6 attacks occurred during the summer months. One attack followed a game of touch football on a relatively warm winter day. On another occasion he lost consciousness while standing over a radiator, clothed warmly. Although it was not possible to obtain measurements of bloodflow, the clinical evidence suggests that his reactions were similar to those of J.K.

It seems likely that, although these patients reacted qualitatively like normal individuals, the additive effects of their tachycardia and vasoconstriction upon standing were inadequate for maintaining the blood pressure.

B. Peripheral Mechanism Impaired by Localized Lesions: In the 2 patients above, the additive effects of both cardiac and peripheral reflex activity appeared to be insufficient for maintaining the level of blood pressure upon standing. A similar inadequacy can result from lesions which affect primarily the peripheral vasomotor nerves. Ellis and Haynes[8] have reported the frequent incidence of orthostatic hypotension among tabetics:

T.S. was a colored man, aged 56, with tabes dorsalis. Dr. Louis Laplace will publish his extensive observations upon this patient elsewhere, but has granted us permission to refer to the abnormalities present. Orthostatic hypotension was found occasionally and unpredictably. Half an hour before and half an hour after the test illustrated by Chart 2-E, the blood pressure was much higher (170/130) and showed no appreciable fall upon standing. Our tests indicate that there was normal acceleration of the pulse and constriction of the finger arteries accompanying the marked fall in blood pressure. Like J.K., he showed normal *thermal* reflex dilatation in his toes. The neurological abnormalities exhibited by this patient lend support to our belief that the occasional failure to maintain the level of blood pressure upon standing may have been due to transiently inadequate vasoconstriction to the lower extremities.

L.M., a white man of 25, was admitted June 11, 1940, to the neurological wards of this hospital, service of Dr. W. B. Cadwalader. Pain and weakness in both lower extremities were disabling, and had persisted after an acute onset in 1936. No arterial pulsations were palpable in the lower extremities. Signs of sensory and motor nerve abnormalities in the lower extremities were interpreted as being caused chiefly by occlusion of the aorta at its bifurcation. Measurement of skin temperatures over the lower extremities indicated an almost total lack of thermal reflex vasomotor activity. This may have been due in large part to thrombotic occlusion, despite skin warmth and color indicative of a good collateral circulation through the smaller vessels. While lying quietly his blood pressure was 138/75, pulse rate 96. Upon standing, the blood pressure fell to 110/70, the pulse accelerated to 120. Transient vertigo was noted upon standing. Examinations of finger bloodflow were not made. We believe that his mild orthostatic hypotension was due principally to deficient vasomotor control in his lower extremities.

V. *Orthostatic Hypotension Associated with Mechanical Defects in the Circulatory System.* If an abnormally great fall in blood pressure can be the result of dysfunction of the sympathetic nerves supplying the heart and blood-vessels, the same abnormality might obtain if there were mechanical defects which would nullify the activity of a normally functioning vasomotor system. Through the courtesy of Drs. W. E. Lee and N. E. Freeman, we are permitted to report our observations upon one of their patients who appeared to illustrate the latter:

B.L., a girl of 17, had a large venous angioma of the right lower extremity extending from the crest of the ilium to the sole of the foot. The right foot was swollen and painful. She was prone to faint upon standing quietly. Physical examination did not reveal important abnormalities other than the angioma. Chart 2, F-1, illustrates the enormous increase in heart rate upon standing, accompanied by a considerable fall in blood pressure. When she stood up, the volume of a small portion of her lower leg increased by 200 cc. In Chart 2, F-2, are shown the results of tying off some of the venous communications of the angioma: the blood pressure did not fall significantly, but reflex vasoconstriction was still more marked than normal. After a second operation, with further ligations, there was maintenance of blood pressure with less vasoconstriction Chart 2, F-3. At this time the volume of the lower leg increased by only 90 cc. from lying to standing. She was entirely relieved of her symptoms.

The orthostatic hypotension found in this patient seems clearly related to pooling of blood in her extensive hemangioma. There was no evidence of inadequate reflex vasomotor activity; on the contrary such activity was more marked than normal, as a compensatory mechanism. Certain other conditions under which pooling of blood is said to occur, such as arteriovenous aneurysm, pregnancy, and large varicose veins, are not often reported to be associated with orthostatic hypotension, perhaps because of a compensatory increase in blood volume: We have observed that a girl of 18, with marked cardiac enlargement due to a patent ductus arteriosus (proved at operation), responded normally to a change from the lying to the erect position.

Discussion. *The Clinical Differentiation of Types of Orthostatic Hypotension:* We have suggested that orthostatic hypotension might theoretically result either from inadequate reflex (*a*) constriction of peripheral vessels; (*b*) acceleration of the heart; or (*c*) augmentation of cardiac output. Our data have not included evidence concerning (*c*). Preliminary observations, using a vertical ballistocardiograph, suggests that immediately upon standing, the cardiac output of normal persons will either fall or remain constant, irrespective of the blood pressure.[17] This would minimize (*c*) as an adaptive mechanism, and would suggest that (*a*) and (*b*) are the more important in maintaining blood pressure in normal individuals under such conditions.

While we have cited finger bloodflow as an indication of peripheral vasomotor activity, it will be seen that one can infer, within limits, the extent of such vasomotor activity from the clinical examination of the pulse and the blood pressure. If the level of blood pressure

is adequately sustained without marked tachycardia, it may be assumed that active vasoconstriction has occurred, as demonstrated in Chart 1. Conversely, if the level of blood pressure falls abnormally associated with marked tachycardia, it is probable that peripheral constriction is inadequate, unless there are mechanical faults in the circulation. This latter response is characteristic of patients who have suffered functional or structural derangement of peripheral sympathetic nerves. Finally, if orthostatic hypotension occurs without commensurate tachycardia, as in the classical cases, it is to be inferred that the cardiac accelerator pathways do not function, but the state of the peripheral sympathetics cannot be evaluated without further evidence, such as can be obtained by measurements of peripheral bloodflow.

As illustrated by the clinical cases presented, the discovery of abnormalities in the central or peripheral nerves, or of vascular thromboses, or arterio-venous shunts, may render more intelligible the interpretation of orthostatic hypotension in any given case.

We suggest, therefore, that a careful clinical examination, in the absence of more elaborate tests, will often suffice not only to diagnose the condition, but also to allow an understanding of the abnormal physiology involved and point the way to effective treatment.

Treatment. The primary objective in the treatment of orthostatic hypotension is to compensate for the tendency of the blood to gravitate to the inferior portions of the body when the patient stands erect.

Various mechanical means have been employed. Victims of this disorder soon discover the dangers of standing quietly. They learn to sway or to shift from one side to the other, as did our patient W. L., so that the pumping action of the muscles can be utilized.[2] Tight abdominal binders are useful. However, W. L. failed to obtain subjective or objective improvement from an abdominal binder alone, whereas there was definite relief when both legs and the abdomen were bandaged tightly. MacLean and Allen[13] have found that symptoms upon arising are less severe in patients having orthostatic hypotension, if they will learn to sleep with their heads and shoulders elevated. On warm days strenuous physical exertion is to be avoided.

The medicinal treatment of severe degrees of this disorder has been generally disappointing, despite some rather optimistic reports.[7,11] It should be emphasized that the low levels of blood pressure at which patients will experience vertigo or syncope may vary considerably according to the individual, the environmental temperature, and the physical activity. It seems likely that the state of the cerebral blood-vessels is also an important factor. A combination of drug actions which would lower the threshold of cerebral activity, while increasing the tone of peripheral arteries and

veins, would seem to be desirable. Such a combination is now available in amphetamine[16] and paredrinol (veritol).[18]

In elderly persons with cerebral arteriosclerosis, symptoms may be experienced when only a slight fall in blood pressure occurs.[19] For these patients, the use of a pressor drug is probably ill-advised. Actually, small doses of amphetamine, without paredrinol, will frequently be sufficient for symptomatic relief. Conversely, in younger patients with severe orthostatic hypotension, the pressor action of paredrinol is probably the most important part of their treatment.

Drugs such as epinephrine and ephedrine will assuredly raise the blood pressure, but are prone to give undesirable, side effects. W.L. could not tolerate even 5 minim doses of epinephrine subcutaneously on account of headache and palpitation. The blood pressure increased from 120/96 to 150/100, but fell to 90/60 when he stood up.

We have observed the effects of amphetamine, paredrine, paredrinol, and the isomeric constituents of amphetamine in the case of W.L. and others. Dr. John A. Reisinger has furnished us with data concerning the effects of ephedrine and neo-synephrin upon W.L. Because of the variability of his blood pressure responses it is difficult to make an accurate analysis of drug action. Suffice it to say that he felt his best, and his blood pressure seemed best sustained, when he took 10 mg. of amphetamine and 20 mg. of paredrinol orally before arising, then repeated the paredrinol at hourly intervals until 4 P.M. No untoward reactions have resulted from a year's medication according to this schedule. Repeated electrocardiograms, taken during trials with various drugs, were most nearly normal as regards *T* wave amplitude when he was taking this combination. During hot summer weather, however, this medication did not prevent the occurrence of attacks of unconsciousness with convulsions if he ventured up from the basement of his home.

Table 1 shows the most favorable responses in pulse and blood pressure obtained in the case of W.L. and others during the time when they were taking the specified drug, or combination of drugs. The least abnormal responses, without therapy, are included for comparison. Because paredrinol, *in therapeutic dosage*, is an almost purely pressor drug, having no disturbing side effects in our experience, we feel that it deserves a further trial in the treatment of orthostatic hypotension. Our experience does not permit a comparison of the clinical effectiveness of paredrinol versus paredrine. W.L. complained less of lassitude when taking paredrinol. It is apparent that in the case of classical orthostatic hypotension, medication sufficient to produce hypertension had to be given. Even then, the tendency of the blood pressure to fall was not abolished. The lower levels reached were still high enough, however, to avert the usual syncopal attacks.

TABLE 1.—EFFECT OF DRUGS UPON CARDIOVASCULAR RESPONSE TO STANDING. BEST RESPONSE, ONLY, TO DRUGS TRIED.

Pt.	Drug.	Dose per day (mg.).	Lying.		Standing.		Vertigo or faintness on standing.	Side effects.
			B.P.	Pulse.	B.P.	Pulse.		
W.L.	None	..	110/90*	80	50/45	90	++	
	Amphetamine	80	145/120	80	70/55	100	0	Insomnia
	d-amphetamine	30	170/115	66	65/55	90	0	Insomnia Headache
	l-amphetamine	30	150/110	78	60/50	90	+	0
	Amphetamine 80 / Paredrine 80		110/90	78	50/?	90	+	Insomnia
	Paredrinol	200	160/110	72	70/60	90	0	0
	Amphetamine 10 / Paredrinol 160		160/118	66	70/58	78	0	0
L.M.	None	..	138/75*	96	112/75	120	+	
	Amphetamine 5 / Paredrinol 120		110/74	90	60/50	150	+++	0
	Amphetamine 5 / Paredrinol 160		126/78	92	92/64	124	0	0
J.M.	None	..	100/60*	66	42/38	144	++++	
	Amphetamine 10 / Paredrinol 60		100/60	54	110/70	90	0	0

* Marked variability from day to day.

It is perhaps only a coincidence that 2 of our patients were found to have basal metabolic rates below the limits of normal. Daily rations of thyroid substance were given to J.M. for 2 years, but it was not felt justifiable to test its effects without the simultaneous use of other therapy. The possibility of contributory endocrine dysfunction should be considered in the clinical evaluation of patients having this disorder, and treatment should be planned accordingly. In the case of W.L., the intramuscular administration of testosterone proprionate, 140 mg. over a period of 8 days, resulted in no subjective or objective change.

Summary and Conclusions. 1. The physiology of adaptation to the erect position is reviewed as the basis for an understanding of orthostatic hypotension.

2. The physiologic importance of peripheral vasomotor activity, plus changes in heart rate, is emphasized.

3. A clinical study of normal subjects, patients following sympathectomy and those with orthostatic hypotension is reported, using chiefly the following criteria: blood pressure, pulse rate, digital bloodflow, and skin temperature.

4. According to their reactions to the tests above, our patients have been classified as having orthostatic hypotension due to slight, or marked impairment of reflex vasomotor function, or to mechanical defects in the circulatory system.

5. These patients showed orthostatic hypotension in association with: lesions of the central and peripheral nervous systems (communicating hydrocephalus, tabes dorsalis, and nerve injury secondary to arterial occlusion); the post infectional state; and venous angioma. In one patient (E.M.) no etiology could be discovered.

6. The clinical evaluation of patients with orthostatic hypotension is discussed and a rationale of treatment is outlined.

We gratefully acknowledge further the permission of the following physicians to make reference to their patients: Drs. F. C. Grant, I. S. Ravdin, E. A. Mallon, Temple Fay, Isaac Starr, F. J. Braceland, and C. C. Wolferth.

The Smith, Kline & French Company kindly supplied us with the following drugs: amphetamine, and its dextro- and levo- forms, paredrinol, and paredrine.

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HYPERTENSION AND THE PRESSOR ACTIVITY OF HEATED EXTRACTS OF HUMAN KIDNEYS.

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Saline extracts of kidneys of hypertensive patients were found by Prinzmetal *et al.*[6,7] to elevate the blood pressure of anesthetized and unanesthetized dogs by a slightly greater average amount than did similarly prepared extracts of kidneys from patients whose blood pressure was normal during life. The variation in the observed

* The expenses of this investigation were defrayed in part by a grant from the Commonwealth Fund for that portion of the work done at the University of Pennsylvania.

pressor responses was marked and the results with normal and hypertensive cases overlapped extensively. Likewise, Harrison *et al.*,[2] and Prinzmetal and Friedman[6] found that simple saline extracts of kidneys from experimentally hypertensive dogs elevated the blood pressure of normal dogs to a greater degree than did extracts of normal dogs' kidneys.

On the other hand, Pickering and Prinzmetal[5] and Beckwith and Chanutin[1] concluded that the extracts of kidneys from experimentally hypertensive rabbits and rats, respectively, exhibited less pressor activity than extracts of kidneys made from normal control animals. The last two observations[1,5] were made with partially purified extracts, avoiding thereby the conspicuous initial fall of blood pressure which is characteristic of most simple saline extracts of kidney tissue[3] and which might conceivably diminish or enhance the later pressor effects.

In view of this uncertainty concerning the pressor activity of kidney extracts it seemed advisable to extend the observations on the pressor activity of human kidney extracts, using for comparison a method of extraction[3] which eliminates almost entirely the initial toxic and depressor effects. Despite these apparent advantages, the results of these experiments have proved to be even less definite than those of Prinzmetal *et al.*,[6,7] and Harrison *et al.*[2] It is of interest, however, that in those few instances in which unquestioned pressor responses were obtained, peripheral bloodflow as measured by skin temperature was not diminished. In this respect the pressor substance in extracts of human kidneys resembles the renin of the rabbits' kidney and the renin-activator-angiotonin system described by Page[4] both of which elevate blood pressure without diminishing cutaneous bloodflow.

Methods and Material. *Preliminary observations on methods of extraction and assay.* (*a*) Grinding the kidney tissue in a colloid mill produced more active extracts than did grinding with sand in a mortar, even when preceded by grinding in a Latapie machine. (*b*) Treatment of the filtered extract with appropriate concentrations of ammonium sulphate, followed by dialysis of the active fractions at pH 7.3 was not appreciably superior to heating at 55° C. for 20 minutes with subsequent filtration. The results with both methods were variable, but the average of ten comparisons favored the simpler heating method. (*c*) Changing the pH of the suspension to as low as 4.0 or as high as 8.0 prior to heating generally decreased, and never increased, the yield of pressor material. The pH of the crude extract was approximately 6.5 and heating at this reaction yielded most consistent results. (*d*) Comparison of nephrectomized and normal rabbits for assay purposes indicated that the former were preferable because pressor responses were not only greater but more consistent, agreeing with many similar observations by others on dogs.

Routine Procedure. Human kidneys were obtained at autopsy within 3 to 18 hours after death, and, in 2 instances, at operation. The entire kidney, or a radially cut portion of the kidney, including both medulla and cortex, was divided into small fragments. Enough 0.9% NaCl solution was added to make a 20% extract based on the wet weight of the kidney tissue. This mixture was ground in a colloid mill for 5 minutes, during which the temperature of the suspension did not exceed 35° C. Part of this 20% suspension was heated in a water bath at 55° C. for 20 minutes and then filtered through two layers of filter paper in funnels also heated to 55° C. This clear yellow or reddish extract was used for assay.

The remainder of the 20% crude suspension was frozen and dried from the frozen state (Cryochem process) for preservation and later use if repeated testing was indicated. For assay, rabbits weighing between 2.2 and 3.7 kilos, were anesthetized by injecting subcutaneously 1.3 cc. of paraldehyde per kilo and a bilateral nephrectomy was performed through flank incisions. Immediately thereafter the femoral artery was cannulated and connected to a Hürthle manometer writing on a smoked drum; heparin was used as the anti-coagulant. After a suitable control period (30 to 45 minutes) 20 cc. of 20% heated extract were injected into an ear vein at the rate of 1.7 cc. per minute by a motor-driven syringe. Ten minutes after the end of this initial injection, 5 cc. of a standard active 10% rabbit kidney extract was injected to determine to what degree prior injection of the human kidney extract had protected the assay animal against the pressor effect of rabbit renin. Ten minutes after this second injection the animal was killed by asphyxia and the maximum blood pressure response to this stimulus recorded, for comparison with the remainder of the record. Only one sample of human kidney extract was injected into each animal. In the early assays dosage was graded according to the body weights of the rabbits, but the results were not any more uniform than those in which a set dose was injected.

In a group of unanesthetized rabbits effects of kidney extract on blood pressure, pulse rate, and skin temperature were observed as previously described in detail.[3] Blood pressures were measured in the auricular artery graphically at intervals of one minute. Injections were made painlessly through a minute T-cannula sewed in a marginal vein of the ear. Skin temperature of the opposite ear was measured by means of a thermal junction to determine whether or not peripheral bloodflow was decreased during the period when blood pressure was elevated.

The 16 "normal" kidneys were obtained at the autopsies of patients who, during life, had blood pressures of 80 to 120 mm. Hg systolic, and 50 to 80 mm. Hg diastolic, and presented no anatomic evidence of renal disease. The abnormal kidneys used can be divided into three groups: (*a*) 7 cases of chronic glomerulonephritis with blood pressures during life ranging from 160 to 190 mm. Hg systolic and from 90 to 136 mm. Hg diastolic; (*b*) 15 cases of benign hypertension with blood pressures during life ranging from 150 to 300 mm. Hg systolic, and from 90 to 140 mm. Hg diastolic; and (*c*) 14 cases of malignant nephrosclerosis with blood pressures during life ranging from 200 to 280 mm. Hg systolic and from 130 to 180 mm. Hg diastolic. The cases chosen for study had histories quite typical of their respective anatomic diagnoses. This last group includes 2 cases of hypertension in which a unilateral nephrectomy was performed because of (*a*) anomaly and atrophy, and (*b*) unilateral pyelonephritis.

Observations. In rabbits the slow intravenous injection of simple saline extracts of normal and abnormal human kidneys was often lethal and almost always strikingly depressor, even after careful filtration and centrifugation. The lowering of blood pressure was

accompanied by conspicuous blanching of the ear, dyspnea, tachycardia, and usually a few convulsive movements before death. Therefore the rabbit appears to be more sensitive than dogs or rats[2,6,7] to the toxic and depressor fractions of these crude extracts. On the other hand, freshly prepared heated extracts of human kidneys did not depress blood pressure and were never lethal when injected immediately after heating and filtration. After standing at room temperature for several hours or in the refrigerator for 24 hours, a previously innocuous extract usually became depressor or even lethal once more. These effects could be abolished again by re-heating.

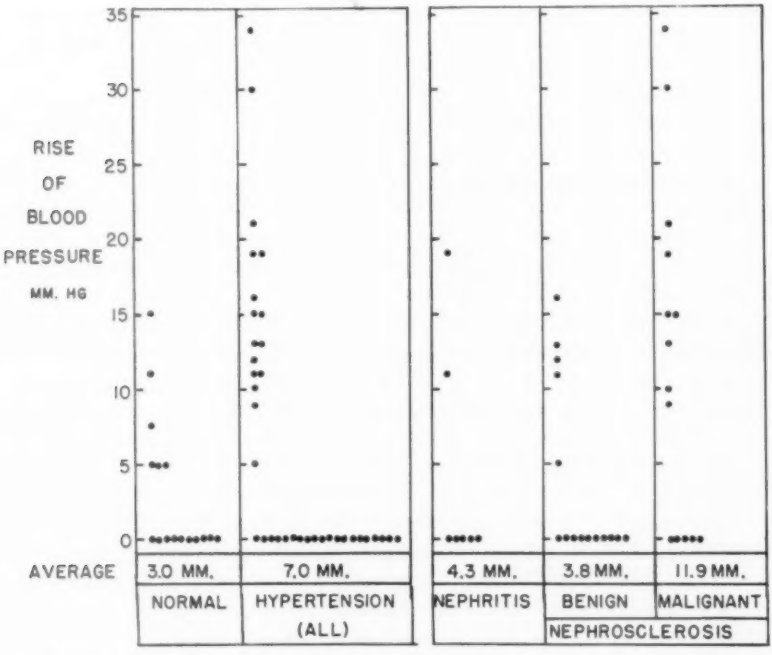

CHART 1.—Pressor activity of heated human kidney extracts, normal and hypertensive cases. To the right the latter are divided into three categories. Each dot represents 1 case.

The heated kidney extracts were either entirely inert producing no perceptible effect on blood pressure or pulse rate, or they were moderately pressor in some instances. Active extracts produced their maximal effect on blood pressure in 2 to 5 minutes; the elevation persisted for 30 to 45 minutes or until the record was interrupted by the injection of rabbit kidney extract at the end of 10 minutes.

The results produced in anesthetized nephrectomized rabbits are summarized in Chart 1. Of 16 extracts prepared from normal kidneys, 10 were inert and the remaining 6 elevated blood pressure by

between 5 to 15 mm. Hg. In the entire hypertensive group, consisting of 36 extracts, 20 were inert, while 16 raised blood pressure by between 5 and 34 mm. Hg. To the right in Chart 1 the hypertensive group has been subdivided according to diagnosis. No difference could be demonstrated in the pressor activity exhibited by extracts of normal kidneys and of those from cases of glomerulonephritis and benign hypertension.

In those cases dying of malignant nephrosclerosis, in the third or fourth decade, 9 of the 14 extracts were active and 5 were inactive. The slightly greater proportion of positive results the greater magnitude of certain of these responses in general, and the higher average observed may conceivably suggest a greater renin content in this group. Yet no quantitative relationship could be demonstrated between the height of the patients' blood pressures during life and the pressor activity of their respective heated kidney extracts. Some of the inert extracts, including the 2 prepared from kidneys removed at operation, came from cases with blood pressure even higher than those providing definitely pressor extracts. While 4, and possibly 6, extracts in the cases of malignant nephrosclerosis produced pressor responses outside the range observed with extracts of normal kidneys, the variation is so great that average figures mean little. Nor did it seem likely that a greater number of assays by this method could produce any more definite conclusion.

As mentioned under *methods*, the injection of human kidney extract into each nephrectomized rabbit was followed 10 minutes later by the injection of a standard dose of heated rabbit kidney extract for the purpose of detecting the presence of protective or anti-pressor effect in the extracts of human kidneys. Extracts from 3 normal kidneys strikingly reduced the effect of the subsequent injections of rabbit renin, but the remainder reduced the effect of the latter injection only slightly or not at all. The extracts from hypertensive kidneys showed similar wide variation of protective effect. The average protection afforded by the extracts from kidneys of hypertensive cases was slightly less than that accorded by the normal extracts, but again the range of variation was too great to conclude that a real difference existed. Nor was there any consistently inverse relation between pressor activity and protective action. Comparison of the pressor and anti-pressor assays with the rise of blood pressure during asphyxia did not modify these conclusions.

Finally, to test the nature of the pressor substance in human kidney extracts, 10 samples which elevated the blood pressure of anesthetized, nephrectomized rabbits by between 10 and 34 mm. Hg were injected also into unanesthetized rabbits. Five of these extracts, though pressor for nephrectomized rabbits, had no effect on the blood pressure of the unanesthetized rabbits, presumably

because of the protective action of normal functioning kidneys. The other 5, however, elevated blood pressure by 5 to 25 mm. Hg, without diminishing peripheral bloodflow. The effects of these few active human kidney extracts were therefore similar to those of renin, as observed previously for heated rabbit kidney extracts[3] and in the renin-activator-angiotonin system described by Page.[4]

Comment and Conclusions. The results indicate that renin is present in small amounts in some human kidney extracts and produces the characteristic rise of blood pressure without reduction of peripheral bloodflow in the rabbit's ear. However, if renin is produced in excess by the diseased kidneys of hypertensive individuals, the inability to demonstrate greater content in those kidneys indicates either rapid passage of the substance into the blood stream, or rapid inactivation after death by autolysis or by substances in kidney tissue which destroy renin. These findings are in agreement with the recent observations of Beckwith and Chanutin[1] in rats. It would appear that present methods, while yielding suggestive results, do not demonstrate any clear relation between blood pressure during life and the renin content of kidney tissue after death. This conclusion does not in any way invalidate the humoral hypothesis of hypertension but emphasizes the necessity of studying active substances in blood during life for clear differentiation.

Summary. Heated kidney extracts were prepared from tissue obtained at autopsies of 16 cases with normal blood pressure during life and of 34 cases with marked hypertension. Anesthetized, nephrectomized rabbits were used for assay. Kidney extracts prepared from cases of benign hypertension and chronic glomerulonephritis were not more active than those of normal kidneys. The four extracts which showed pressor activity outside the normal range all came from cases of malignant nephrosclerosis. Nevertheless, the variations in activity, even in this group, make it impossible to demonstrate by these methods any clear relation between blood pressure during life and the renin content of kidney tissue after death.

The rise in blood pressure produced by active extracts of human kidneys is similar to that observed with renin from other species in that the blood pressure of the unanesthetized rabbit rises without a decrease of peripheral bloodflow.

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SUSTAINED HYPERTENSION FOLLOWING EXPERIMENTAL UNILATERAL RENAL INJURIES. EFFECTS OF NEPHRECTOMY.* †

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Wilson and Byrom[12] were able to produce sustained hypertension as well as necrotic vascular lesions in rats by partially occluding one renal artery. We have also produced prolonged hypertension, using a different type of renal injury, and in addition found that the blood pressure, once elevated, does not quite return to the initial level after resection of the injured kidney.

Method. Albino rats weighing between 120 and 175 gm. were used in this experiment. Hypertension was produced by enveloping one kidney loosely in a V-shaped strip of cellophane.[7,8] At the same time a thin slice of the pole of the opposite kidney (less than 10%) was removed for microscopic examination in half of the animals. Some of the rats died after developing hypertension or were sacrificed for histologic studies. Those surviving were observed for a period of 1 to 6 months. The cellophane wrapping together with the inclosed kidney was then removed through an abdominal incision under ether anesthesia and the changes in the blood pressures recorded for another period of 1 to 4 months.

A control series of 24 rats was studied for the effects on the blood pressure of unilateral nephrectomy with and without biopsy of the opposite kidney. Similar observations were made on 5 male rats whose testes were enveloped in cellophane.

Urea nitrogen in the blood was determined by a gasometric urease method suitable for whole blood.[8] Values for normal rats with this method ranged between 10 and 30 mg. per 100 cc.

The blood pressure was measured in the tail by means of the plethysmographic method of Williams, Harrison, and Grollman.[11] With standardized precautions for heating the animals we have found this method to be efficient and accurate.

The blood pressure usually began to rise within 14 days after application of the cellophane, attaining in about 60 days a peak which was maintained with slight fluctuations for a period of at least 6 months or as long as the injured kidney remained *in situ*. The maximum pressure level was determined by the average of all consecutive readings for a period of 3 weeks

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† We wish to acknowledge with gratitude the technical assistance of Mr. Joseph Marcus.

at the peak of the curve. The maximum rise in blood pressure was calculated as the difference between the maximum blood pressure level and the average preoperative blood pressure. The level after nephrectomy was computed by taking the average of all of the readings beginning 3 days after operation. The course of the blood pressure in a single representative experiment is shown in Figure 1.

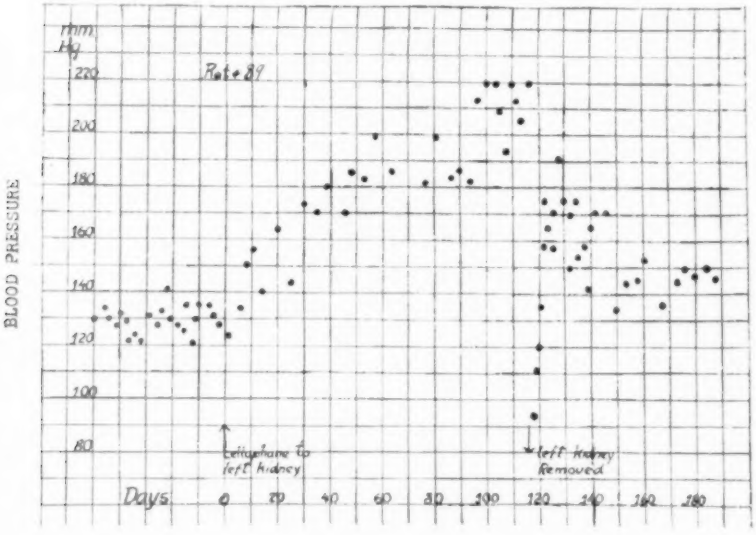

FIG. 1.—Hypertension due to cellophane perinephritis and maintenance of elevated pressure after nephrectomy.

Results. The pertinent data on 91 rats are recorded in Table 1. The maximum rise in blood pressure following unilateral cellophane perinephritis ranged from 0 to 100 mm. Hg (mean, 44 mm.). The hypertension was maintained in most of the animals throughout the period of observation, the longest period being 6 months. Failure to develop sustained hypertension was generally associated with one of the following conditions: tearing or slipping of the cellophane envelope; too tight application of the cellophane resulting in complete ischemic necrosis of the kidney; and emaciation or illness.

The cellophane-wrapped kidney was successfully removed from 44 rats. The blood pressures, if previously elevated declined promptly after operation, but seldom attained the pre-hypertensive level. Usually they remained elevated at varying points as high as 30 mm. above the average initial pressure. Frequently dense perinephric adhesions led to considerable trauma and shock during nephrectomy. In these instances a sharp fall in blood pressure occurred immediately after operation followed by a gradual rise to a point up to or above the pre-hypertensive level, and in one rat (No. 81) above even the hypertensive level. The detailed readings

TABLE 1.—HYPERTENSION AND VASCULAR LESIONS FOLLOWING UNILATERAL RENAL INJURIES AND CHANGES IN BLOOD PRESSURE AFTER REMOVAL OF THE INJURED KIDNEYS.

Rat.	Average initial B.P. level, mm. Hg.	After wrapping one kidney in cellophane.			After removal of cellophane-wrapped kidney.		Vascular lesions.
		Maximum rise in B.P., mm. Hg.	Duration of hypertension, days.†	Urea N, mg. per 100 cc.	Change from initial B.P. level, mm. Hg.	Period of observation, days after nephrectomy.	
1*	132	0	75				
2	124	1	64	...	...	...	0
3	127	6	103	...	...	...	0
4	134	7	88	20			
5*	129	7	90	36	− 4	73	
6*	138	10	90	30			
7	140	10	137				
8	140	10	117				
9*	139	11	28	...	+ 1	120	
10*	135	12	120	19	+ 6	51	0
11*	144	14	64	...	− 3	120	
12*	154	14	77				
13	140	15	90	...	− 1	120	
14	130	15	115	...	...	...	0
15	127	17	89				
16	138	22	34	...	+ 7	60	
17*	120	23	85	...	+ 9	90	
18*	133	25	131	...	+10	62	0
19*	134	25	67	...	+ 8	120	0
20*	122	28	65	...	+ 9	120	0
21	120	29	131	...	+ 9	68	0
22*	136	29	70	...	+14	117	
23*	135	30	70	...	...	...	0
24*	135	30	40				
25	112	30	37	17			
26	137	30	31	...	...	...	0
27*	137	31	62	19	+15	44	0
28	121	32	30	31			
29	121	32	24				
30	127	33	112	13	+25	40	0
31	136	34	101	...	+ 6	40	0
32*	134	34	90	18	+23	45	0
33*	126	34	116	14	+11	45	0
34*	144	35	56	...	+12	45	
35*	139	35	94	...	...	...	0
36*	135	35	16				
37	128	35	34	...	...	...	0
38	125	35	128	17			
39*	140	36	69	...	+ 4	35	0
40*	121	37	140				
41*	133	38	63	16	+19	120	0
42	121	39	94	15	+21	42	0
43*	139	40	100	21	+17	20	0
44	123	41	38	...	...	...	0
45*	144	44	64	18	+22	120	0
46*	142	44	13				
47	141	43	101	18	+12	48	0
48	130	44	107	17	+22	45	0
49	140	45	107	13	+ 7	40	0
50	130	45	189	...	+20	72	
51*	133	44	65	15	+15	120	0

TABLE 1.—*Continued*

Rat.	Average initial B.P. level, mm. Hg.	After wrapping one kidney in cellophane			After removal of cellophane-wrapped kidney.		Vascular lesions.
		Maximum rise in B.P., mm. Hg.	Duration of hypertension, days.†	Urea N, mg. per 100 cc.	Change from initial B.P. level, mm. Hg.	Period of observation, days after nephrectomy.	
52*	145	45	40	18	...	...	+
53*	139	46	122	21			
54	116	46	130	31	...	...	+
55	131	47	41	...	...	...	0
56	130	47	107	12	+ 8	41	0
57*	130	47	110	27	+ 7	39	0
58	121	49	48	...	...	...	0
59	128	50	17	..	...	...	+
60*	130	51	115	...	+16	72	0
61	125	52	111	22	...	...	0
62	128	52	34				
63	128	52	10	...	...	...	+
64	127	53	25	...	...	...	0
65*	141	54	36	...	...	...	0
66*	139	54	64	...	+13	115	
67*	129	55	35				
68	135	55	111	...	+30	40	0
69	110	55	163	...	+18	72	
70	115	56	220	146	...	...	0
71	141	59	53	36	...	...	0
72	129	61	25	28	...	...	+
73*	144	63	65	20	...	...	+
74*	127	65	50	35	+13	60	0
75*	120	62	65	...	+22	96	0
76	158	67	38	20	...	...	+
77*	131	69	75				
78*	73	71	60	17	− 1	115	0
79*	127	73	71	...	...	...	+
80*	124	61	118	...	+28	105	0
81	136	74	93	23	+72	30	+
82*	132	76	80	15	+17	6	+
83*	134	76	60	...	+30	120	
84	120	77	97	25	...	...	+
85*	114	78	77	...	+15	92	
86	110	80	80	17	...	...	+
87*	117	80	41	16	+29	70	0
88*	132	82	36	20	...	...	+
89	128	87	100	19	+30	56	0
90	122	98	90	17	...	...	+
91*	135	100	51	78	...	...	+

* Biopsy taken.
† Rats 1 to 15 from operation to death.

in 3 animals are shown graphically in Figure 2. In 5 instances there was observed after nephrectomy a decline or no change as compared with the initial blood pressure. Four of these (Nos. 5, 9, 11, 13) occurred in rats with little or no rise in pressure after application of cellophane.

The height of the blood pressure after nephrectomy in the hypertensive animals seemed in general to vary directly with the severity

of the preëxisting hypertension. This is illustrated graphically in Figure 3, which plots the relation in each animal between the maxi-

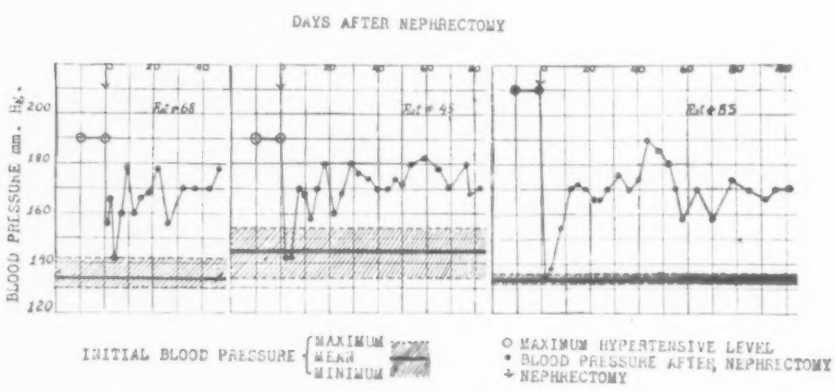

FIG. 2.—Changes in blood pressure following removal of the affected kidneys in rats with hypertension due to unilateral renal injuries.

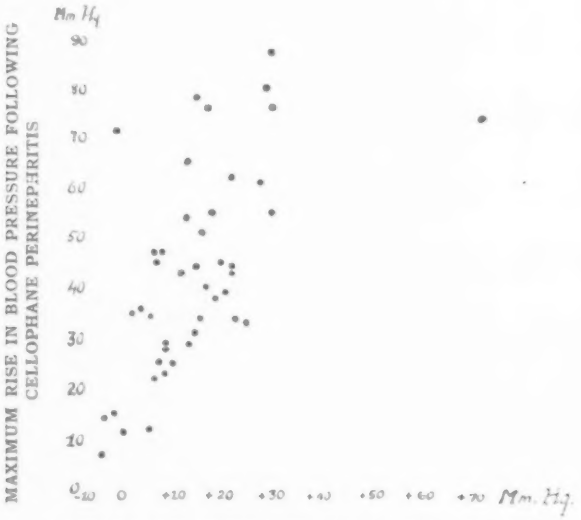

FIG. 3.—Relationship between the blood pressure level after removal of the injured kidney to the severity of the preëxisting hypertension.

mum rise in pressure following renal injury to the change in pressure over the initial level after excision of the injured kidney.

The duration of hypertension, within the limits of this experiment

did not appear to influence the level of blood pressure after nephrectomy. Equally marked effects were observed in rats with hypertension of 30 days, as in those of 120 days' duration.

Twenty-four control rats (12 of which had had preliminary biopsies of one kidney) showed no tendency toward an increase in blood pressure level when a completely intact kidney was excised (Fig. 4). No changes in blood pressure were noted in the animals with periorchitis due to cellophane.

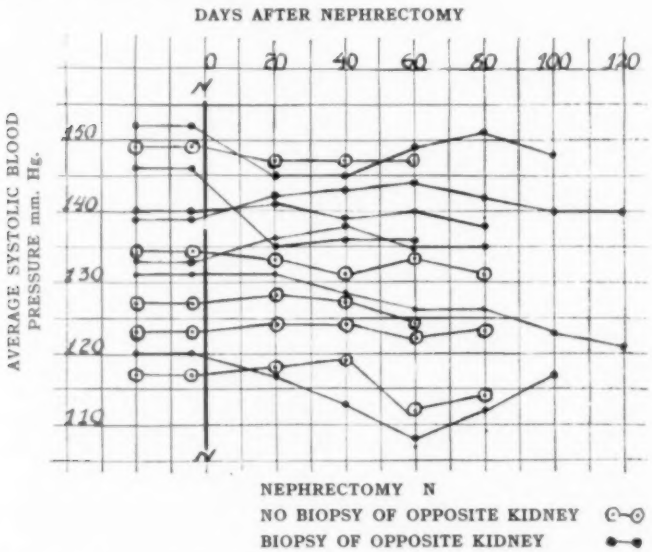

FIG. 4.—Changes in blood pressure following nephrectomy in normal rats.

The kidneys which were enclosed in cellophane appeared considerably reduced in size despite the development of a dense perinephric capsule. Inflammatory invasion of the cortex resulted in varying degrees of interstitial nephritis. Hyalinized, necrotic and inflammatory vascular lesions were observed in 20% of the rats involving the medium sized and small arteries and arterioles of the pancreas, mesentery, intestines, heart, testes and of the unoperated kidney (Fig. 5). No arterial lesions were found in the lungs or in the kidney within the cellophane capsule. The intense inflammatory and necrotic arterial and arteriolar lesions were confined to the animals that had had a severe and rapid rise in blood pressure (more than 45 mm. Hg). Their presence did not appear to be related to the duration of hypertension or to the degree of renal insufficiency. Of the 12 rats with severe vascular lesions in which tests for urea nitrogen of the blood were carried out only 2 showed values for urea above the normal limits. One rat (No. 70) had marked nitrogen retention without vascular lesions.

The vessels in the intact kidneys of the hypertensive animals that survived nephrectomy were compared with those of normal rats (and in some cases with those in the place of their own kidney removed as biopsy). Striking differences were observed in only 2 instances.

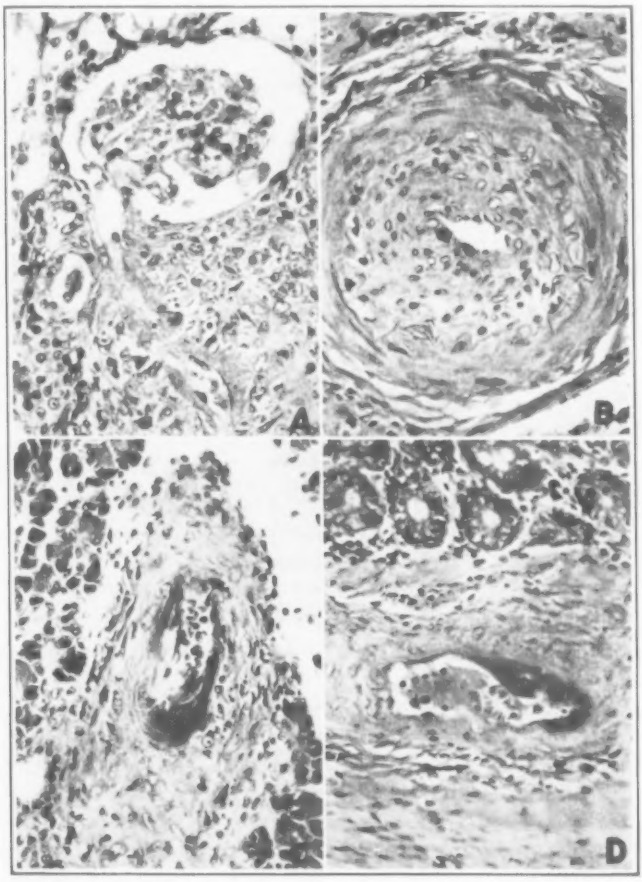

FIG. 5.—Vascular changes in rats with hypertension due to unilateral renal injury. *A*, Intact kidney. Hyalinization of an afferent arteriole. H & E stain. (× 260.) *B*, Intact kidney. Cellular intimal proliferation of a small interlobular artery. H & E stain. (× 260.) *C*, Pancreas. Subintimal fibrinoid necrosis of small artery. H & E stain. (× 260.) *D*, Intestine. Subintimal fibrinoid necrosis of a small submucosal artery. H & E stain. (× 260.)

Discussion. The effectiveness of the cellophane envelope in producing hypertension may be attributed to a combination of factors exercising varying rôles in different animals: 1, Constricting effect of the dense perinephritic capsule; 2, constricting action on

the hilar structures with arterial, venous, and ureteral obstruction; 3, prevention of collateral circulation through the cortex; 4, inflammation of the kidney substance due to a foreign body.

Our observations with cellophane are in complete agreement with those of Wilson and Byrom[12] who employed arterial clamps. Sustained hypertension as well as arterial lesions may be produced in the rat by an injury to one kidney using either method, the contralateral kidney remaining intact. In these respects the findings in the rat appear to differ from the general experience with experimental hypertension in the dog and rabbit. Prolonged hypertension resulting from unilateral renal lesions was observed in occasional dogs by Goldblatt[3b] and Wood and Cash[13] and in rabbits by Drury.[2] They did not note severely hyalinized and necrotic vascular lesions in animals with an intact kidney.[3a,9] Our data indicate that the presence of renal insufficiency is not an essential factor for the development of these lesions. They agree with those of previous observers,[3a,9,12] who emphasized the importance of a rapidly developing severe elevation of blood pressure.

Maintenance of an elevated blood pressure after removal of the injured kidney in a hypertensive animal has not previously been reported. It cannot be attributed to loss of kidney substance because it did not occur in nephrectomized non-hypertensive rats. We did not observe significant rises in blood pressure levels over a period of one year in normal rats of a corresponding age group, so that changes due to ageing may be considered negligible. Grossman and Williams[4] recorded blood pressures by direct arterial cannulation in rats varying in age from 2 months to $2\frac{1}{2}$ years and found no consistent differences in this range. The influence of cellophane as a foreign body may be disregarded, since the changes did not occur in all the animals and were not noted in rats with similar injuries to the testicles.

The new level of pressure after nephrectomy does not represent a transitional phase between the hypertensive and normal points. It was sustained for a period of 3 or 4 months or longer, showing no tendency to decline and occasionally even rising gradually toward the hypertensive level.

The persistence of an elevated pressure long after the original stimulus has been removed suggests that irreversible changes have been induced. We have no evidence concerning the nature of these alterations other than those previously described in the vessels. The presence of arterial and arteriolar lesions in the unoperated, presumably normal kidney may serve to establish new areas of renal ischemia; while their occurrence in an extensive splanchnic vascular bed may act as a contributing factor in maintaining an elevated blood pressure. The findings of Blalock and Levy[1] are of interest in this connection. They succeeded in producing complete occlusion of the cœliac axis and the superior and inferior mesenteric arteries in

dogs and noted a sustained elevation in blood pressure in some animals.

Extensive anatomic changes in the vessels were seen in only a small fraction of our animals and may have no causal relation to the elevated blood pressure. It is conceivable that an increase in peripheral resistance might occur due to narrowing of the vascular bed which is too minute to be detected microscopically. The resistance to flow varies inversely as the square of the radius of the vessel, so that a small change in lumen can effect a proportionately larger change in resistance.

There have accumulated in recent years a number of reports bearing on the association of hypertension with unilateral renal disease in humans and on the course of the blood pressure following excision of the diseased kidney. Schroeder and Fish[10] reviewed the cases in the literature and added 7 of their own. Additional cases were reported by Nesbit and Ratliff[5] and by Oppenheimer, Klemperer and Moschkowitz.[6] All authors agree that nephrectomy was frequently followed by symptomatic improvement. A decline in blood pressure was observed often after operation but was either transient or else rarely attained a level which could be considered normal for the patients' age. Of the 28 subjects reported all but 6 remained actually or potentially hypertensive after nephrectomy.

In this respect the observations in humans parallel those in our hypertensive rats. Neither in the experimental animal nor in the hypertensive patient with unilateral renal disease can one expect to obtain a "normal" blood pressure by removing the diseased kidney. We do not imply that nephrectomy is therefore bound to be fruitless as far as the hypertension is concerned. On the contrary, evidence presented indicates that an injury to a single kidney, resulting in hypertension, may lead to systemic changes which operate independently of the injured kidney in a manner to maintain an elevated blood pressure.

Summary. 1. Sustained hypertension was produced in rats by means of unilateral renal injury (perinephritis from enveloping the kidney in a cellophane envelope).

2. Hyalinized and necrotic vascular lesions were observed in some animals. Their presence was associated with rapidly rising severe hypertension but was not related to the duration of hypertension or to the presence of nitrogen retention.

3. Removal of the injured kidney from the hypertensive animals resulted in a decline in blood pressure, not to the pre-hypertensive level, but to some point above it depending upon the severity of the hypertension. Maintenance of an elevated pressure long after removal of the injured kidney suggests that irreversible changes have occurred which may or may not be related to the changes in the vessels.

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THE GERIATRIC ASPECT OF PULMONARY TUBERCULOSIS.

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It is unwise to make elaborate studies of pulmonary tuberculosis in the younger and healthier fractions of the population while neglecting the old age groups where contact is known to exist. Tuberculosis in these older persons reflects the presence of yesterday's epidemiology in today's society.

At present, the average fatal case of pulmonary tuberculosis occurs in an individual who is several years older than he would have been if the sequence of events had occurred a generation ago. The graph of tuberculosis mortality shows a falling peak in early years and rising peaks in later decades. The swing of the disease across the age span requires recognition in order to reduce the dispersion of the infection from old to young, and to elaborate methods of attacking the disease in the older individual. It would seem as if the infection, slowly being thwarted as a disease, is making headway in old tissues because methods successfully applied in young persons are not as adaptable in the older person. Every new case of tuberculosis is a demerit chalked up in vital statistic records to signify that there are still unstopped loopholes.

There is no question of the frequency of pulmonary tuberculosis in the higher ages. However, it is quite possible that the type of management in this group may constitute one of the most important obstacles to eventual success in curtailing the disease generally. The particular elements common to the older age bracket may be summarized as: the different reaction of the older body to the

tubercle bacillus; the longer period in which the infection may have been present; economic considerations; the welfare of the younger members of society; the general difficulties in controlling older patients; and the lack of an efficient medical and social approach to this problem. If to those growing old, pulmonary tuberculosis is an insidious personal matter, it still remains one of the major unsolved health problems of the present day. Any effective approach to this problem must eliminate the present common attitude of simply sighing at the aged tuberculous patient with positive sputum.

This study includes 3000 consecutive postmortem examinations done at the Philadelphia General Hospital during 1936 and 1937. Of the group reviewed, about one-third were 60 years and over, totalling approximately 1000 individuals. The ratio of white to negroes above 60 was 3 to 2. The male and female groups were approximately equal in number.

For general statistical application, pulmonary tuberculosis was classified as: 1, fibro-ulcerative; 2, miliary; and, 3, healed fibroid. The less usual varieties of the active form were incorporated in these groups to avoid over-elaboration. Taubert,[24] found all forms of the disease in the higher age group. Stanganelli[23] gives a much fuller classification, but the purpose is served by using the three groups named.

Excluding the primary tuberculous complex in the series, it was found that tuberculosis of the lungs occurred in 757 patients, which is 25% of the general dead that came to autopsy in the period mentioned.

In the *fibro-ulcerative group* of 462, there were 52 patients (11.2%) in the age bracket of 60 years and over. Schlesinger[22] in a series of 1800 autopsies, found that 9% of active tuberculosis occurred in older persons. The important unknown is: how much tuberculosis is disseminated in the general population by this 11.2%? If the figures were applied to the general population, it would indicate that 5% of all persons 60 years and over have active tuberculosis (*i. e.*, 52 in 1000 general autopsies) though of course it is recognized that our material does not constitute a fair sampling of the population (see Table 1).

TABLE 1.—FIBRO-ULCERATIVE GROUP.

			Ratio of whites to negroes.					
			Over 60 1000 autopsies.			Under 60 2000 autopsies.		
	Total.	Under 60.	Over 60.	No. auts.	With tb.	Corrected.	No. auts.	With tb.	Corrected.
Total	462	410	52	3:1	3:1	1:1	3:2	2:3	4:9
White	200	160	40						
Negro	262	250	12						

In the *miliary group* (referring only to miliary pulmonary tuberculosis and not to the more common terminal miliary spread) there

were 60 patients, of whom 51 died of the disease. Of this number, 5 were 60 years and over, an incidence of 8.3%. Both Banyai[1] and Baudot[2] regarded this form as rare in older persons, while Braun[3] found an incidence of 14%. von Rosen's[26] figure for the occurrence of the miliary type in general autopsies was 0.5% to 1.5%. Rich[20] and Follis observed that "miliary tuberculosis tends to be a much more frequent complication of pulmonary tuberculosis in old age than at any other period of adult life." The present figures show that one older person in 200 has miliary tuberculosis, in agreement with the limits of von Rosen's statistics.

TABLE 2.—MILIARY GROUP.

			Ratio of whites to negroes.					
			Over 60 1000 autopsies.			Under 60 2000 autopsies.		
	Total.	Under 60.	Over 60.	No. auts.	With tb.	Corrected.	No. auts.	With tb.	Corrected.
Total	60	55	5	3:1	3:2	1:2	3:2	1:6	1:9
White	11	8	3						
Negro	49	47	2						

The figures show that this form of tuberculosis does not spare the older patient since one-twelfth of the total number occurred in the higher age group. The older negro is less prone to this form than is the younger of his race, but is more liable to have it than is the white member of his own generation. The young white is far less liable to the miliary form than is the young negro.

In the *healed fibroid group*, there were 235 patients. The cause of death in order of frequency of occurrence was heart disease, cancer, pneumonia, cerebral vascular accidents, and renal failure. In those of the fibro-ulcerative group who did not die of tuberculosis, cancer was more common than heart disease as the cause of death. Of the 235 patients, 153 (65%) were 60 years and over. If this figure could be applied to the general older population, it would signify that 15 of every 100 persons 60 years and over has healed fibroid pulmonary tuberculosis. This is in accurate agreement with Schlesinger's findings.[22]

TABLE 3.—HEALED FIBROID FORM.

			Ratio of whites to negroes.					
			Over 60 1000 autopsies.			Under 60 2000 autopsies.		
	Total.	Under 60.	Over 60.	No. auts.	With tb.	Corrected.	No. auts.	With tb.	Corrected.
Total	235	82	153	3:1	9:1	3:1	3:2	2:1	4:3
White	192	55	137						
Negro	43	27	16						

In summary, these figures reveal that a fair percentage of both fibro-ulcerative and miliary pulmonary tuberculosis and a very large percentage of the healed fibroid form, occurs in persons 60 years and over. As to race, there is no difference in the fibro-ulcerative,

predominance to a slight degree of the miliary in the older negro, and marked predominance of the healed fibroid type in older white persons.

The keynote of the geriatric approach to pulmonary tuberculosis is that there has not been general appreciation of the frequency of the disease in older persons.[1,2,4,8,10,13,16b,17–19,21–24] It is interesting that Osler's[19] studies were made at this hospital a half century ago. He wrote that "at the Philadelphia Hospital, in the wards of aged persons from the almshouse, it was extremely common to find either old or recent tuberculosis." The reason for such frequency is due to the combination of three contributing groups: 1, those in whom the disease was diagnosed in early life, treated successfully, and obtaining a normal tenure; 2, those in whom there was no early diagnosis due to self-neglect or inadequate study; and 3, those in whom there were no marked clinical manifestations of the disease until later life, or who contracted the disease then. Of the third group, it may be that the tuberculosis is of recent date, but due to the changed physiology of the elderly body, it evokes a proliferative rather than an exudative response. Such a body response could make *recent* disease look like an *old* condition. Banyai's[1] fine study begins on the note that old age changes alter the type of body reaction. Probably it is true that the disease may be carried through life in various phases of activity or inactivity, or that it may be contracted in later life with altered response to the infection. The three groups enumerated include all forms. It is not to be inferred from this that reference is being made to the initial entrance of the tubercle bacillus into the body, but rather to that form which is the usual clinical manifestation of the disease.

Having established figures at this hospital for the incidence of pulmonary tuberculosis in older persons by comparison with the younger group, and correcting the ratios for racial differences, we investigated the protocols of 136 individuals 60 years and over who had been diagnosed as tuberculous and studied on the tuberculosis wards.

Family History. Of the 136, 80 had noted the family history more completely than a few routine questions. Thirty-five (26%) reported known tuberculosis in older members of the family. In Myers'[17] group of 37 patients, the family history was positive in 24% for the preceding generation, and in 35% of the following generation. Roentgen examination of 173 persons 65 years and over in a New Jersey County disclosed 13 persons with active pulmonary tuberculosis, one of whom had 14 Mantoux positive grandchildren.

Symptoms. There is a tendency toward understatement of the manner in which pulmonary tuberculosis presents itself in the older patient. In some, the clinical picture is as vivid as that observed in the younger decades; in others, there may be few or no symptoms. Is it necessary to recognize a new façade to this old structure, or

will old landmarks serve? The following is a tabulation of the symptoms of this group:

	Per cent.
Cough	95
Expectoration	87
Loss of weight	82
Fatigue and weakness	72
Dyspnea	68
Hemorrhage	46
Loss of appetite	42
Night sweats	35

With the exception of hemorrhage and night sweats, any or all of the other complaints could be ascribed to the debilitation of increasing age. It is quite likely that this facile conclusion is responsible for the failure to diagnose cases. The diagnostician must become conditioned to the thought that if he is dealing with this train of symptoms in an older person, his consideration of pulmonary tuberculosis should be as automatic as it would be if the story had been presented to him by a younger person.

Temperature. Of the charts reviewed, 51% showed an elevation of temperature of at least several days' duration during the course of the hospital stay. Many discrepancies can enter into the evaluation of fever in the elderly. The following are the commonest sources of error: the few times in a 24-hour period when the temperature is recorded, self-observation, and most important of all, the fact that the readings were oral, whereas accurate temperature observation in older persons can be obtained best by rectal thermometry. Banyai[1] felt that fever did not occur as often due to slower toxin absorption via narrowed lymphatics, poor stimulus and lessened irritability of the thermal center. Calmette[4] found that chronic pulmonary tuberculosis in the aged was possible without fever. Ichok[8] noted that febrile attacks were rare. Joress[10] and Rubin,[21] on the other hand, are inclined to the relative frequency rather than to the infrequency of this symptom.

Roentgen Study. Of the total number, 128 had Roentgen ray studies and in each the clinical opinion was confirmed. The distribution of the lesion from the report of the film was:

	Per cent.
Involvement of both upper lobes	45
Involvement of right upper lobe alone	17
Involvement of right lung and left upper lobe	11
Involvement of left lung and right upper lobe	7
Involvement of entire right lung	5
General involvement of both lungs	7
Miscellaneous other than above	8

Where the roentgenologist noted the type of lesion, a diagnosis of the fibroid form was made in 56%, one plate was read as miliary, and the remainder were grouped as fibro-ulcerative. In 60% cavitation was reported. Banyai[1] found 43.9% of moderately advanced and 52.5% of far advanced cases to have cavitation. Joress[10]

reported an incidence of cavitation by Roentgen ray reading in 43%. The corroborative value of the Roentgen ray in each of these patients is important because of the view expressed by Myers[16a]; "our studies have led us to look on the Roentgen ray film of the chests of children as almost a total waste as far as tuberculosis is concerned." After this period of life, however, he urges the widespread use of Roentgen ray. In the old chest many changes may have occurred that will mislead, but on the whole the picture of pulmonary tuberculosis together with all other findings make a definite diagnosis.

Sputum. It is important in the control of tuberculosis to determine just how many elderly individuals with active lesions produce sputum which contains tubercle bacilli. In this series, the report was positive in 69%. No figures can be given as to how often during a period of years in which the patient had tuberculosis, known and unknown, the sputum was positive or negative. Undoubtedly spontaneous conversions occur, but when or how often cannot be said. It is unfortunate that, unless some check with periodic sputum examination is made, it cannot be known when elderly patients with the disease, 95% of whom cough and 87% of whom have expectoration, are dangerous to those with whom they live.

In Banyai's[1] group the sputum was positive in 79.1%. In Meade's[15] small series, the positive percentage was 61. Myers[17] reported 56% in his list, and Joress[10] 44%, with the note that "undoubtedly a greater incidence of positive sputum cases would have been found if other methods (besides the ordinary stained-smear examination) had been employed." Making a study of a large number of individuals in an old-age institution, not particularly suspected of any disease, Goldmann and Wolff[6] found an incidence of 2% of positive sputum. A recent repetition of this work in Italy[25] found 3 cases positive in 198 persons in a home for the aged. On thoroughly studying these 3, they were found to have pulmonary tuberculosis with such a bland clinical complex as to justify the opinion that they were well. So much for the individual; the positive sputum is another matter. Certainly where the Roentgen ray is so frequently correct, and the sputum positive in 69%, a diagnosis should not be difficult.

Symptoms of Onset. As a guide to differential diagnosis, it should be noted in what manner the abnormal condition first presented itself to the patient.

In order of frequency the following symptoms of onset were recorded:

	Patients.
Cough	29
Common cold	23
Pleurisy	9
Weakness	8
Hemoptysis	6
Dyspnea	3
Nausea, night sweats, pneumonia, nervousness	each 2
Heart trouble, hiccoughs	each 1
No particular symptoms	20

For the most part, the onset appeared to be innocuous and diagnosis had to wait upon a continuation of such symptoms beyond any ordinary expected period of time, or for the development of more alarming complaints, or even for other cases in the family to occur to require investigation.

Tuberculin Test. We have no figures for the tuberculin test in this group. In the literature there are conflicting views. Kereszturi, Goldberger, and Nojima[11] performed the intradermal tuberculin test using 0.1 mg. O.T. on 353 white persons, age 40 to 92, and found that 96% were positive. These persons were similar to our group, namely, urban dwellers of the lower economical stratum. They concluded that "disappearance of tuberculin allergy with advancing age is rare." It might be predicted that with the general fall in the distribution of tuberculous infection the use of the tuberculin test in older persons will become increasingly important. Of course when clinical impressions and Roentgen ray readings are equivocal, the tuberculin test together with every other form of examination that may aid, must be used.[7,12]

Diabetes Mellitus. It was found that 15 (11%) of this group had both pulmonary tuberculosis and diabetes mellitus. In Rubin's[21] group the incidence was 17%. All of our diabetic patients had positive sputum. Twelve (80%) had a Roentgen diagnosis of cavitation. Since there is a greater incidence of cavitation (80% as compared with 60%) and of positive sputum (100% as compared with 69%) in the diabetics, it is indicated that these patients must be more carefully observed because the average elderly diabetic is usually a home-body, thus increasing the chance of spread of the pulmonary disease in the family. Certainly diabetes mellitus in older patients with tuberculosis increases the gravity of the case. In Joress'[10] group, where there was an incidence of 13.3% of diabetics among his tuberculous patients, 37% of the total mortality occurred in this fraction. In our series, death occurred in 52% of the 136, but among the diabetics the mortality was 60%.

Therapy. Of this group only 6 (4.4%) had more than bed or ambulatory hospital care. In 2 there were phrenic operations. In the remaining 4 pneumothorax was attempted, in 1 of whom it was completely successful, 1 developed marked hydropneumothorax, and in 2 it failed to be induced. It is generally felt that treatment too often is too conservative. However, the pthisiologist who does pneumothorax should follow the lead of those surgeons who are evaluating their older patients closely so that needed surgery can be done when indicated. This surgical attitude has been summarized by Mayo and Nettrour[14]: 1, careful evaluation of the condition and reserve of the patient; 2, individual preoperative planning, assuming sufficient skill to perform the task with the least risk; and, 3, careful attention to detail which, to the highest degree that can be obtained, is the secret of success in surgery of the aged. These postulates

are completely applicable to the case when pneumothorax is considered.

Discussion. Those who have studied pulmonary tuberculosis in the higher age group are impressed with the lack of emphasis on this phase in the study of the disease. A flank attack on this weak spot would circumvent more circuitous methods to the same end, namely, the lessening of the general incidence of tuberculosis. Jennings[9] sums up the matter thus: "the prevalence of tuberculosis in the older age groups has not been stressed in proportion to the vital aspects of the situation as a public health problem." Drolet's[5] warning that the incidence of the disease is falling without a proportional drop in mortality is not cheering. This mortality ratio has persisted in the face of increasingly radical procedures. The inference is that isolation, rest, and careful case control have stood the physician in better stead in handling the disease in gross than any method elaborated to handle the disease in individuals. A reduction in general morbidity means a lowering in general mortality. The older unrestrained and infectious members of society must be found and controlled to prevent their continuous contribution to the chain of tuberculous infection.

Isolation of the old positive-sputum patient, however, presents a gigantic problem. This responsibility is not strictly speaking that of the sanatoria because the aged tuberculous patient may not be amenable to active therapeutic measures, nor is he readily adaptable to a sanatorium regimen. A sympathetic public has never refused to support anything pertaining to child health, yet prevention of tuberculosis in children is so definitely associated with the isolation of the child's tuberculous progenitors that the measures in vogue at present are a generation tardy. Institutionalizing children from infected homes in preventoria and returning these same children to their homes without removing the source of the infection is not only epidemiologically futile but also harmful therapeutically. The removal of the old tuberculosis carrier from his home is as a matter of fact usually difficult, and may require the enactment of special state measures to effect its accomplishment.

The establishment of separate communities for old tuberculosis carriers close to large municipalities or on the grounds of the state sanatoria would be an interesting and not too costly experiment for one of the large states to undertake. After the initial outlay, the cost of maintenance plus the possible general lessened incidence of the disease would be less than the support of these patients in the more expensive general hospital, to say little of the benefits to the state of a falling tuberculosis rate. Prior to the withdrawal of such individuals from active communal life, each would be reviewed by those expert in the disease to render an opinion as to whether more active treatment could be given. Otherwise these homes would be limited to the older tuberculous patient for whom we as yet have no

procedure that will render him safe to his community. As compensation to the patients there would be comfortable homes, gardens, minor occupational therapy and association with those of their own age and times. The public would be served in having a reduction in the incidence of tuberculosis by the stoppage of a major source of the disease at its very origin.

Summary. In 3000 routine postmortem examinations done at the Philadelphia General Hospital, it was found that pulmonary tuberculosis was present in 25% of the patients. The older age group, 60 years and above, comprised one-third of the total necropsy figure, and in this fraction there was 28% of the total incidence of pulmonary tuberculosis. Included in this 28% were 11% of the fibro-ulcerative, 8% of the miliary, and 65% of the healed fibroid form of pulmonary tuberculosis.

If the tuberculosis figures could be applied to the general older age population, it would appear that in persons over 60, 5% have fibro-ulcerative, 0.5% have miliary, and 15% have healed fibroid pulmonary tuberculosis. A comparison by race showed that the active form of the disease was equally as common in elderly whites as in elderly negroes, that the miliary form was somewhat more common in the elderly negro, and that the fibroid form was much more common in the elderly white person.

The symptom complex is quite like that seen in younger persons, but may be obscured by the changes of increasing age, or be interpreted as due to senile debility. Cough and expectoration were the most common complaints, but hemorrhage, fever, and night sweats were not uncommon. As a rule, the symptoms of onset of the pulmonary condition were mild.

In a study of 136 hospital protocols of older persons who were in the tuberculosis division of the Philadelphia General Hospital, there was a positive family history in 26%. The Roentgen ray report confirmed the clinical impression in every case where it was used, and recorded cavitation in 60% of the patients. In 69% there was a positive sputum by the routine stained smear method. In the diabetics who composed 11% of this group, the sputum was positive in each case, and cavitation was reported in 80%.

Active therapy was negligible.

Conclusions. The fact that pulmonary tuberculosis is not uncommon in elderly persons seems to fail to impress both the public and the physician, possibly due to the nature of the older body affected by a chronically progressive disease. The actual incidence would indicate that this large group is a major obstructive feature in the national tuberculosis program of segregation of open cases. In brief, what is needed is earlier diagnosis, coupled with more stringent isolation and more active treatment. Such a program would tend to lessen the general incidence of the disease and also to do more for the older person so afflicted. Increased emphasis on the geriatric

factor in tuberculosis would benefit not only the older patient but the general population.

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V. HUMAN CONSTITUTION AND SYPHILITIC INFECTION.

A Review of the Literature, a Projected Method of Study, and Preliminary Results in 36 Patients.*

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In the several centuries preceding the development of serologic tests for syphilis and modern antisyphilitic treatment, it was generally assumed that every person infected with syphilis and untreated therefor ultimately developed some lesion of late syphilis. With the then existing lack of laboratory diagnosis, many infected patients were unrecognized as such; and in those recognized, the progress of the infection could be followed on a clinical basis only. Moreover, then as well as now, treatment for all patients recognized as syphilitic was the universal rule, and the course of the infection was more or less profoundly modified by this factor.

Not until 1929, with the publication of Bruusgaard's[4] important study, was any accurate information available concerning the spontaneous evolution of syphilitic infection in untreated persons.

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For the first time, it became clear that the course of syphilis was widely variable. In approximately equal proportions, in persons observed in the absence of treatment over many years, four general types of evolution of the disease were observed: 1, spontaneous "cure," *i. e.*, complete freedom from all detectable clinical, laboratory, and even necropsy evidence of the disease; 2, prolonged latency, *i. e.*, no clinical evidence of disease manifestations due to syphilis, but the persistence of laboratory evidence of infection manifested by positive serologic tests of the blood; 3, the development of apparent allergy, the sensitization of the patient to his own treponemes, and the explosive appearance of allergic gummatous benign late syphilis, involving chiefly skin, mucosæ, bones, and eye; and, 4, the very gradual evolution of the degenerative and potentially crippling or lethal late lesions of cardio-vascular or neurosyphilis.

Quite obviously, it would be of major importance in the individual management of syphilis, if not in its public health control, if the eventual course of syphilitic infection in each of these four directions could be anticipated in the patient at the moment of his infection. Both type and amount of treatment might be profoundly modified if one could predict that Patient A, just infected with syphilis, would succeed, even without treatment, in controlling his own infection completely, while Patient B was a candidate, even with standard treatment, for the eventual development of disabling or fatal syphilitic disease.

This study was planned as a study of certain factors which might influence the course of syphilitic infection in the individual patient.

Possible Reasons for Variations in the Course of Untreated Syphilitic Infection. We may consider three variables: 1, the infecting organism; 2, extraneous factors, such as intercurrent disease, nutritional deficiencies, pregnancy, and so on; and, 3, the defense mechanism of the host.

The Infecting Organism. There has been much clinical speculation and some experimentation as to whether variations in virulence of strains of *T. pallidum*, or variations in the size of the inoculum, might produce corresponding variations in the course of syphilis; but neither in human beings nor animals has any convincing proof of either of these hypotheses been adduced.

Aside from strain virulence *per se*, there is some clinical evidence suggesting the "tropism" of certain strains of treponemes for the nervous system of human beings. The suggestion has been made that there may be "neurotropic" and "dermotropic" strains, though tropism for other body tissues has not been even clinically identified. Unfortunately, it has not proved possible to confirm these reputed strain variations in the laboratory in a satisfactory manner.

Nevertheless, variation in strain of organism must be kept in mind as a possible, perhaps even probable, explanation of variation

in the course of the infection, though proof of the hypothesis must wait upon the so far unaccomplished successful cultivation on artificial media of virulent *T. pallida*.

Extraneous Factors. The influence of intercurrent disease, especially intercurrent infection, on the course of syphilitic infection cannot be accurately evaluated. In associated tuberculosis and syphilis, there is some evidence, not too convincing, of effect of one upon the other (Padget and Moore[19]); but in other associated diseases, there is only the vaguest speculation.

Only two extraneous factors can be implicated as even a probable influence on the course of syphilis: pregnancy and nutritional deficiency. It seems reasonably clear that in some as yet unidentified manner, pregnancy exercises a favorable influence on syphilitic infection (Moore[15a,b] and Kemp[12]); and at least probable that nutritional deficiency, especially of vitamin A, B, or both, may predispose to the development of certain forms of neurosyphilis, especially tabes dorsalis (Moore and Woods[17]).

No extraneous factor can be suggested, however, to account for the variable course of untreated syphilis as observed in an entire syphilitic population.

The Defense Mechanism of the Host. It is quite clear to the student of infectious disease that human beings vary enormously in susceptibility to many of them, and in the severity of their manifestation. At one end of the distribution scale is a small group of "non-susceptibles," rarely if ever attacked by acute infections, and if so only mildly ill; at the other, an equally small group of "susceptibles," prone to many infections and seriously affected by all of them. The majority of the population stands midway between these two extremes.

The explanation for this epidemiologic phenomenon appears to lie within the individual and to be dependent on factors loosely embodied within the term "human constitution."

As applied to syphilitic infection, this inherent variability in human constitution does not extend, as with certain acute infections, to natural immunity against infection, since, so far as is known, all human beings are susceptible; but it seems the most likely explanation of the variable course of disease in infected persons.

The literature on the relationship of human constitution to disease is already vast and rapidly growing. No attempt will be made to review it in detail. We point out only that emphasis is shifting from the anthropologic and anthropometric approach of earlier workers (cf. especially Draper[6]) to a more purely biologic approach. To many workers, including ourselves, it seems probable that whatever the relationship between bodily habitus and degenerative or metabolic diseases may be, this relationship can hardly be as clear cut to infectious diseases, acute or chronic. Here the relationship must depend upon inherent biologic factors, such as, for example,

the variable ability of different persons to produce antibodies to organisms or antigens. There is as yet no clear cut evidence that "biologic constitution," if one may coin the phrase, is related to "physical constitution."

Even the literature on the relationship of human constitution to syphilitic infection is so large, so vague and diffuse as almost to defy adequate discussion. There are, for example, many studies, especially recently from our own clinic, which show quite clearly that race (Turner[25] and Zimmermann[26]) and sex (Turner[25] and Moore[15a,b]) profoundly modify the individual's reaction to *T. pallidum*. In many respects, from the predominating type of early tissue reaction to the relative incidence of such late manifestations as cardiovascular or parenchymatous neurosyphilis, syphilis differs in the Negro and white races. Both in experimental animals and human beings, syphilitic infection is milder in females than in males. These facts have been repeatedly observed, but as yet there are neither definite information nor adequate hypotheses as to why they should be so.

Excluding from further discussion these two factors of race and sex, the literature is fortunately summarized (discursively) in two monographs: to 1929, by Königstein and Wertheim,[13] and to 1937 by Curtius, Schlotter, and Scholz.[5] From them, the following discussion is drawn.

Certain clinical facts seem clearly agreed upon, and are related by most observers to "human constitution." There is no proof of "complete innate immunity" to syphilis in human beings, though such a suggestion is contained in the observation (Brandt[3]) that prostitutes who have not acquired the disease within the first 3 years of practice rarely do so later. There are frequently repeated combinations of several syphilitic symptoms (*e. g.*, the association of iritis, the folliculo-papular syphilide, and hydrarthrosis in Negroes with early syphilis) or of involvement of paired organs (cochlear nerve lesions). An extensive early tissue reaction (florid early secondary syphilis) seems to protect the patient against the subsequent development of parenchymatous neurosyphilis; while conversely, paresis and tabes tend to occur in those whose outward evidence of early tissue reaction was minimal or lacking. Likewise, benign late (allergic gummatous) syphilis rarely precedes or is associated with parenchymatous neurosyphilis. The disease is always more severe in floridity of early lesions and in incidence and extent of gummatous late lesions in "virgin soil," *e. g.*, a population into which it has just been introduced, than in a population in which it has been present for many years.

Hereditary factors have been studied; and there is some evidence, not very convincing, that "degenerative," *i. e.*, parenchymatous, neurosyphilis is more frequent in families in which other degenerative diseases of the nervous system tend to occur.

It has been repeatedly suggested, but never proved, that syphilis acquired at an advanced age is more serious than in early adult life.

Many attempts have been made to link body habitus with cardiovascular and neurosyphilis. Neusser[18] thought that "hypoplastic" individuals are particularly disposed to the localization of syphilis in the aorta but according to J. Bauer[2] and to Bartel,[1] the "digestive" and "muscular" types are those particularly disposed to aortitis. While they used somewhat different classifications of habitus, Stern,[24] Hirschl-Marburg,[11] and Rasdolski[21] are reported to be in essential agreement regarding the relation of habitus to paresis and tabes; they found that paretics tended to be hypersthenic and tabetics hyposthenic. Gyárfás,[10] in a small series, reported reverse findings.

Königstein and Wertheim[13] summarize some of their own investigations on constitution and syphilis. They state that their results are based on an investigation of 10,000 cases but give few specific data. They use the classification of habitus as normal tonic (sthenic), hypertonic (hypersthenic), hypotonic (hyposthenic) and occasionally use also the term asthenic. They believe that papular eruptions and leukoderma are most frequent among hyposthenics; alopecia is more frequent with hyposthenics and sthenics; recidive eruptions are most common with hypersthenics; malignant syphilis (report based on 36 cases) occurred oftenest with hyposthenics and next oftenest with hypersthenics. They also tried to correlate spinal fluid abnormalities in secondary syphilis with habitus but found no essential difference between the different body types. They do report that hyposthenics with papular exanthems had a definitely higher incidence of spinal fluid changes than did sthenics with the same type of eruption. They attempt a correlation of some manifestations of early syphilis with hair color and report that recidive eruptions and alopecia are more frequent with blonds than with brunettes, while the reverse holds true with leukoderma.

Königstein and Wertheim mention several observers who have found that the rapidity with which seroreversal occurs under treatment can be correlated with blood group. Persons belonging to group "O" become seronegative most rapidly; those belonging to group "A-B" most slowly.

Since 1929 a number of articles have been published dealing with constitution and syphilis, particularly in the European literature. Most of these contribute little to the subject but some are worthy of mention.

Reiter[22] in 1929 carried out experiments to test the hypothesis that relative and absolute disposition to infectious diseases is based on certain constitutional metabolic peculiarities. He selected cholesterol metabolism as the factor to investigate and syphilis as one of the diseases. He conducted experiments on a limited number of human syphilitics and on a still more limited number of

rabbits. His conclusion was that the growth of *T. pallidum* is favored by high cholesterol content. However, he found what he considered to be evidence that the blood cholesterol of patients who had developed neurosyphilis (mostly paresis or tabes) were lower than the average. He extended his hypothesis to include this observation by assuming that in individuals with syphilis and low blood cholesterols, the conditions in the tissues generally are relatively unfavorable for *T. pallidum*, so the organisms seek out organs with high cholesterol content, in this case, brain and spinal cord. His recorded data are not at all convincing proof of his conclusions.

Dujardin[7] first (1922) advanced the theory that the type of syphilis a patient might ultimately develop could be determined by intradermal test with horse serum (0.2 cc.). His theory was based on his doctrine of "hetero-allergy" and his belief that individuals who developed gummata were allergic and those who developed paresis and tabes were anergic. His doctrine of hetero-allergy was that an organism sensitized to one specific antigen is at the same time sensitized to other non-specific antigens. Accordingly, a patient who was about to develop gummatous syphilis would react intradermally with horse serum as well as with luetin, while the reverse would hold true with paresis and tabes. Sézary and Coumetou[23] in 1930 reviewed Dujardin's publications[7,8a,b] and presented convincing evidence that neither the hypothesis nor the observations were correct.

Perkel and his associates[20] in 1930 inquired into conditions predisposing to the development of cardiovascular syphilis. They regarded inadequate treatment, particularly in the early stage, as the most important factor; but also believed that constitution (habitus and "underdevelopment and weakness of the cardiovascular system") and unfavorable influences in the environment were important. Of their patients with cardiovascular syphilis, 67.5% were of the pyknic habitus.

Lazarovits[11] in 1932 reported on the rôle of constitution in the development of late syphilitic changes, particularly aortitis. He investigated 200 men and 100 women, supposedly selected only in the sense that they had had the disease for at least 10 years unless they had already developed late manifestations. He compared the outcome of the disease with habitus (Kretschmer's classification) and concluded that the pyknic type showed the most tendency to the development of aortitis.

Guirdham[9] in 1936 investigated the body type of the general paralytic in 27 patients with paresis, using both Pignet's measurements and Pignet's index calculated from Kretschmer's average figures. He concluded that variations in weight in paresis were sufficient to change the classification. He also concluded that his data do not afford a basis for assuming that any one type is

predisposed to paresis, but does not preclude the possibility that paretics are relatively more pyknic than tabetics.

Curtius, Schlotter and Scholz[5] carefully studied a group of 101 tabetics and their families, and by the same methods, a control series of 200 cases of non-tabetics and their families. They found that while there was no significant difference in the two groups as far as body type was concerned, there was a correlation between body type and the severity of tabes. Tabes tended to be more severe in the slender (asthenic) individual than in the more broadly built (hypersthenic) individual. That the asthenic habitus was not the result of tabes they attempt to show by early photographs of patients and by examination of their families. Tabetics more frequently had neurologic and psychiatric disorders antedating the development of their tabes, and their families a higher incidence of epilepsy, feeble-mindedness and psychoses than the control series. Tabes, and particularly "rudimentary" tabes, was commoner in the families of tabetics, while other forms of central nervous system syphilis were not. These authors investigated other factors, such as the vegetative nervous system, the arrangement of capillaries in the nail bed, endocrine glands, blood picture, blood type, allergy, and so on, without finding significant differences between the test and control groups. They do not consider the possible relationship between tabes and nutritional deficiency.

Method of Study. In spite of the vagueness of results achieved thus far, it seemed advisable to study the problem of the relation of constitution to the course of syphilis by a biologic rather than an anthropologic approach. To eliminate the factors of race and sex, whose effect on the course of syphilis is well known, the study was limited to white males who had developed the following types of syphilis: 1, late latent syphilis of 15 to 20 years' duration; 2, gummatous syphilis; 3, degenerative—fibrotic syphilis: (*a*, cardiovascular; *b*, tabes or paresis). The patients were also to have had no treatment—particularly in the early stage—or wholly inadequate treatment. Data gathered on them included a detailed history of the syphilitic infection, the number and severity of other infectious diseases they had experienced, active and passive immunization and allergy. Information was also secured on positive physical findings, necessary routine laboratory work (including routine serologic tests for syphilis, spinal fluid findings, Roentgen ray studies of heart and aorta) and special investigative laboratory data. These special data included quantitative Wassermann tests, results of revaccination with cowpox, luetin tests, blood group, horse serum sensitivity, Dick test, Schick test, and quantitative tuberculin test (clinical and roentgenologic evidence of tuberculosis being absent in all). In order to facilitate the gathering of data, special blanks with designated spaces for different data were printed and were filled out on

each patient studied in the investigation. (Copies of the recording blanks are available on request.)

As the study progressed it became apparent that the rigid criteria set up for the selection of material made it difficult to secure patients, particularly in a clinic whose clientele was predominantly Negro. The criteria were therefore relaxed somewhat to permit the selection of patients whose late latent syphilis was of only 10 years' duration; and patients with gummatous or degenerative late syphilis were selected even if they had had a good deal of treatment, provided it was administered late enough in the course of the infection not to have influenced the immune state to any great extent (*i. e.*, after the fourth year). In spite of these relaxations it was not possible to secure enough suitable patients in the period available for the study to provide real statistical significance.

Technical Details of Study. The Roentgen ray studies of heart and aorta included fluoroscopy and posterior-anterior and left anterior oblique teleroentgenograms. The quantitative Wassermann tests represent titered Eagle complement fixation tests. In the revaccination tests with cowpox, vaccinoid as well as vaccinia reactions were recorded as positive; the tests were done with the "multiple pressure technique." The luetin tests were performed with "organic luetin" furnished us by Dr. George W. Raiziss of the Dermatological Research Laboratory. Horse serum sensitivity was tested for intradermally by the injection of 0.1 cc. of 1 to 100 dilution and ophthalmically by the instillation of several drops of a 1 to 10 dilution of normal horse serum. The quantitative tuberculin tests were performed with recently prepared dilutions of "old tuberculin."

Results. The results of the study are presented in Tables 1 and 2. Data are presented on 7 patients with late latent syphilis, 10 patients with gummatous syphilis, and 19 patients with "degenerative-fibrotic" syphilis. Of the 19 patients in the latter category, 6 had tabes, 4 taboparesis, 6 paresis, and 3 had cardiovascular syphilis.

In Table 1 are summarized the data from the study of the patients relative to the frequency and severity of past infectious diseases and to allergy. No conclusions are permissible, though it is suggested that the severity and frequency of the acute infectious diseases are higher in patients with long-standing latent syphilis than in those with various late manifestations.

In Table 2 are summarized the results of the various tests for immunity done on the patients. As was to be expected, the incidence of positive luetin tests was highest in patients with gummatous syphilis; in contradiction of Dujardin,[7,8a,b] there was no relation between skin sensitivity to luetin and to horse serum; in confirmation of Moore and Eagle,[16] there was no relation between quantitative Wassermann titer and type or severity of disease. For the other observations enumerated, the number of cases reported is too small to justify conclusions.

Discussion. The purpose of this article is to emphasize a method of approach and to encourage others to attack the problem from

TABLE 1.—HISTORY OF INFECTIOUS DISEASES AND ALLERGY.

Type of syphilis.	No. of patients.	Average infectious "disease index."	Extremes of "disease indices."	Allergy in patient.	Allergy in family.
Late latent	7	13	9–18	1 definite 2 history urticaria on one occasion 1 history of eczema?	2
Gummatous . . .	10	6	0–17	3 definite 1 history urticaria on one occasion	0
"Degenerative fibrotic" (cardiovascular, tabes, paresis)	19	7	0–18	1 definite 1 history migraine	1 definite 1 history migraine

In taking history of infectious diseases on each patient an attempt was made to estimate the severity of each disease by the 1, 2, 3, 4 grading system. "Disease index" was determined for each patient by the addition of severity indices of infectious diseases which patient had suffered.

In the 7 patients called "Late latent," the classification of 2 could be questioned. In 1 case, a lumbar puncture could not be obtained; in the second case the patient had been classified as "Late latent" but a subsequent examination revealed the residuum of a juxta-articular nodule and a history of 2 others which had disappeared with treatment.

In the "Gummatous" group, there was 1 patient in whom the history was unreliable, partly on account of language difficulty. If he is omitted there are 9 patients with disease index of 7.

In the "Degenerative-fibrotic" group, 8 of the 19 patients had histories of infectious diseases which were none too reliable. If they were omitted, there are 11 patients with an average "disease index" of 9. Also in this group, 9 of the patients with neurosyphilis had apparently had some arsenical treatment fairly early in the course of the disease which might have influenced them to develop at least a more serious type of neurosyphilis.

TABLE 2.—TESTS OF IMMUNITY.

Type of syphilis.	No. of cases.	Results of tests.								
		Revaccination with cowpox.	Luetin test.	Blood group (Moss).	Horse serum sensitivity.	Dick test.	Schick test.	Quantitative tuberculin test.	Wassermann titer.	
									Average.	Extremes.
Late latent	7	4—pos.	3—pos.	3—II 2—III 1—IV (1 not tested)	1—pos.	1—pos.	2—pos. 1—pseudo	3—1:10 M 4—1:M	5	0–25
Gummatous	10	7—pos.	6—pos. 1—? (KI?)	3—II 3—III 1—IV (3 not tested)	No pos.	4—pos.	3—pos. 1—comb.	4—1:10M 5—1:M 1—1:100	19	0–100
"Degenerative fibrotic" (tabes, paresis, cardiovascular)	19	7—pos. (3 positives uncertain of previous vaccination) (1 not tested)	4—pos.	2—I 4—II 2—III 9—IV (2 not tested)	No pos. (3 not tested)	4—pos.	6—pos. 3—comb.	1—1:100M 8—1:10M 8—1:M 1—1:M neg. 1—100 neg.	19	0–150

this angle. It is admitted that because of the rigid criteria for the selection of patients and the limited period of time available for the study, the number of patients here studied is not large enough to give statistical significance to differences in data.

The ultimate aim of such a study is the securing of data sufficient to enable one to predict the eventual outcome of infection in an individual with syphilis if he is untreated early in the course of his disease. This might allow real individualization of treatment. Patients with poor prognoses might be given more and perhaps different treatment than others, and other clues might enable the supplementing of ordinary methods of treatment.

In the patients of this study, the immunologic background to other diseases has been emphasized. Added desirable observations would be antibody production to bacterial (*e. g.*, typhoid vaccine) and foreign protein (*e. g.*, egg white) antigens. There are of course no present means of testing qualitatively and quantitatively for immunity against syphilis; and the mechanism of antisyphilitic immunity may well not be comparable to that of most infectious diseases. The evidence so far available indicates that immunity in syphilis is predominantly tissue rather than humoral, and perhaps more comparable to immunity in tuberculosis than to that in acute infectious diseases. Possession of more knowledge of immunity in syphilis and ways to test for it would be invaluable and should facilitate to a great extent the study of constitution and syphilis, and the development of methods of prognostication.

Summary. The literature on the human constitution and syphilis has been briefly reviewed. A method of attack on this problem has been outlined and the potentialities emphasized. Data from cases studied in this manner have been presented.

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THE CEPHALIN FLOCCULATION TEST IN CIRRHOSIS OF THE LIVER.

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In previous reports a flocculation reaction has been described which is usually positive in diseases characterized by diffuse inflammation of the liver parenchyma.[1a,b] Details of the test have been described elsewhere. In brief, it consists of adding an emulsion of cephalin and cholesterol to diluted serum and noting the degree of flocculation and precipitation after 24 and 48 hours. The serum of normal subjects gives a negative test. Likewise, the sera of patients with disease of the bile ducts or chronic passive congestion of the liver usually give negative tests,* whereas cases of hepatitis (catarrhal jaundice) give positive reactions during the active stage of the disease.

It has already been indicated[1a] that the test may be either positive or negative in cases with cirrhosis of the liver. It is inferred from studies on hepatitis that there may be concomitantly active injury to the liver cells in this disease. Cirrhosis, however, may be entirely quiescent; the scarring indicating a healing of some injury in the past. In such cases a positive flocculation would not be expected. With these assumptions in mind, the sera of a group of patients with cirrhosis of the liver were tested at various stages of their clinical disease.

For the past 4 years cirrhosis of the liver has been investigated by one of us (A. J. P.) at the Research Service of the First Medical Division at the Welfare Hospital, New York City. The beneficial

* A recent publication by Pohle and Stewart[3] reports positive flocculation in many cases of chronic passive congestion of the liver and obstructive jaundice. The cephalin employed by these investigators was used directly after preparation and is obviously more sensitive than that used in the present studies. Our cephalin is aged in the air and sunlight for about 6 weeks until it becomes dark brown and gummy in consistency.

effects of a highly nutritious diet supplemented by vitamin B concentrates has already been reported[2] and more detailed analysis of these cases is now in preparation. In brief, the clinical progress in this cirrhosis group can be classified as follows:

1. *Favorable.* A significant number of patients show clinical improvement. This is characterized by gain in weight and strength, permitting the patient to resume his usual activity; by disappearance of ascites, edema, and jaundice without recurrence; by changes of serum proteins, bromsulfalein dye test, and Takata-Ara test towards normal values.

2. *Equivocal.* This group is composed of patients who show only partial clinical improvement for months or years. They do not recover robust health. Certain of these die apparently from "simple failure" of the liver. In other instances a fatal relapse is precipitated by intercurrent disease.

3. *Unfavorable.* Certain patients continue a progressive downhill course despite all forms of therapy.

We are reporting briefly a correlation of the cephalin flocculation reaction with the clinical course in a group of 40 selected cases of cirrhosis of the liver chiefly of the alcoholic type, some of whom have been followed 3 years or longer. Detailed descriptions of the clinical features are not included as they are to be presented by one of the authors elsewhere. Chemical data also are not reported here although the course of the disease was followed repeatedly with serum protein studies, bromsulfalein determinations, icteric index values and Takata-Ara reactions.

It has been impracticable to conduct the cephalin flocculation studies in a systematic manner in all instances. In certain cases the initial test was not performed until after a favorable trend had been established. In others only a single determination was made because of the rapid demise of the patient. In the majority, however, a test was made approximately every 3 months. Readings were strikingly consistent from time to time and any changes marking a trend in the reaction were usually gradual unless an acute episode intervened.

The 40 cases of hepatic cirrhosis are presented in Table 1, according to the type of the cephalin flocculation reaction: those with persistently strong reactions (++++ and +++); those with diminishing reactions over a course of months or years; those with persistently negative or weak reactions (neg. and +).

TABLE 1.—CORRELATION BETWEEN THE CEPHALIN FLOCCULATION REACTION AND THE CLINICAL COURSE OF 40 PATIENTS WITH CIRRHOSIS OF THE LIVER.

Intensity of flocculation reaction.	No. of cases.	Died.	Stationary or unfavorable course.	Favorable course.
Persistently strong	17	12	4	1
Progressively diminishing	12	3	0	9
Persistently weak or negative	11	3	0	8

Twelve of the 17 cases with persistently strong reactions presented in Table 1 have died. Seven of these had a rapid downhill course. In 5 cases an initial improvement was poorly maintained, and it was followed by relapse with the return of ascites, jaundice, and ultimate death. Of the 5 living patients, 4 are doing poorly, whereas 1 appears to be in good health. The latter case is somewhat atypical, since the patient is a non-alcoholic, and since his cirrhosis is complicated by myxedema.

The outcome has been considerably more favorable among the 12 patients who have gradually developed weaker flocculation reactions. Many of this group, when first observed, were indistinguishable clinically from the more severe cases. However, their course after entry to the hospital was more favorable. Relapses seldom were observed. Although there were 3 deaths in this group, only one instance was directly attributable to cirrhosis of the liver. This patient, who had shown marked improvement, died from a massive hematemesis following an alcoholic spree of several weeks. In some instances the flocculation test changed along with the general clinical improvement, while in others there was a lag of 6 or more months before serologic differences were detected.

There are also listed 11 cases which had weak or negative flocculation tests persistently. Eight of these have had a favorable clinical course. In this group 3 showed marked improvement before the initial tests were done. It is possible that they would have shown positive tests at the onset, and might therefore have been classified with the preceding group.

However, 3 patients in this group have died. At autopsy, one showed moderate portal cirrhosis together with extensive portal and mesenteric vein thrombosis. There is suggestive evidence that the other 2 deaths were not due to liver failure. Unfortunately autopsies were not done. One of the patients in this group, apparently with typical cirrhosis, has shown an unusually sluggish recovery from liver failure. There remain, therefore, 4 instances in which a negative test possibly may have been misleading as an index of a quiescent disease process.

Initial tests (Table 2) on the sera of our patients show that there is no correlation between the flocculation reaction and the presence or absence of ascites. However, in the presence of jaundice and ascites, or of jaundice alone, the test is rarely, if ever, negative.

TABLE 2.—CORRELATION BETWEEN THE CEPHALIN FLOCCULATION REACTION AND SYMPTOMATOLOGY IN 40 PATIENTS WITH CIRRHOSIS OF THE LIVER.

	Total No. of cases.	Strongly positive, ++++, +++.	Moderately positive, ++, +.	Weakly positive or negative, +.
Ascites and jaundice	14	7	7	..
Ascites alone	13	6	2	5
Jaundice alone	4	2	2	..
No jaundice, no ascites	9	2	2	5
No. of cases	40	17	13	10

These findings are supported by many isolated observations on other patients with cirrhosis of the liver of the Laennec type. Negative reactions are occasionally encountered, however, in cases of biliary cirrhosis with jaundice where intrahepatic obstruction of the bile ducts is a feature.

Discussion. There are numerous tests that reveal changes in one or another function of the liver, but there are few that aid in gauging the severity of the disease process in terms of life expectancy. From the limited number of observations in this study, it appears that in patients with cirrhosis of the liver the prognosis is grave when the flocculation test is persistently positive. On the other hand, the change from a positive to a negative test in a patient may be regarded as a favorable prognostic sign. Although the data are too few to be conclusive they suggest that the flocculation test may be of value in prognosticating the course of this disease. It is hoped that further application of the test will define more clearly the limits of its usefulness.

We have observed that the diagnosis of cirrhosis must be made with reservations when the flocculation test is constantly negative. For example, a number of cases of presumptive cirrhosis because of ascites, have eventually proved to be Pick's disease, thrombosis of the portal vein or neoplasia of the peritoneum. In several instances, also with negative flocculation reactions, cases with esophageal or gastric varices have been observed in which no lesions in the liver were present at operation or autopsy. Hepatomegaly with negative flocculation reactions is commonly observed in alcoholic subjects. These cases are often mistaken for cirrhosis, but occasional biopsies indicate that the underlying lesion consists of fatty infiltration of liver cells rather than parenchymal disintegration with replacement by connective tissue. It is not yet determined whether cirrhosis is an end stage of these fatty changes or whether the fatty liver is especially subject to damage by unfavorable conditions that may coëxist. Our observations with the cephalin flocculation test favor the latter view, for positive reactions seldom appear in cases of fatty liver unless inflammatory or acute degenerative changes are also present.

Conclusions. The cephalin flocculation test has been employed in 40 cases of cirrhosis of the liver that have been treated with a highly nutritious diet supplemented by vitamin B concentrate. A correlation has been made between the clinical course of these patients and the intensity of the reaction.

1. The ultimate prognosis in patients with Laennec's cirrhosis showing persistently strong positive reactions is not favorable, irrespective of apparent clinical improvement.

2. Progressive decrease in the intensity of the cephalin flocculation reaction often accompanies clinical improvement and a return

of blood proteins to normal values. Relapses in this group are relatively uncommon.

3. A negative reaction does not exclude the diagnosis of cirrhosis. However, patients with persistently negative tests tend to have a relatively favorable course.

4. The intensity of the flocculation reaction does not parallel the presence or absence of ascites in cases of cirrhosis of the liver. However, no cases of alcoholic cirrhosis with jaundice have been encountered giving a negative reaction.

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CAUSES OF PAINLESS GASTRO-DUODENAL HEMORRHAGE.

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Hematemesis, melena or both, unattended by pain is a common enough observation. Recurrences are the rule, the hemorrhages come without warning and in the intervals symptoms referable to the gastro-intestinal tract are absent or trivial. The diagnosis of duodenal ulcer is conventionally made. As soon as the patient's condition warrants, a gastro-intestinal Roentgen ray examination is done and the usual findings are negative, or at best reveal a slight deformity of the duodenal cap. If such a deformity is reported, the diagnosis of duodenal ulcer is considered clinched. If the Roentgen ray is reported negative, the ulcer is regarded either as healed, or not sufficiently physically pronounced, or so situated that it escapes recording on the Roentgen ray film. Such a case constitutes one of the commonest of hospital records under the classification of "bleeding duodenal ulcer."

It is obvious that such a case may not be considered closed because there are many causes for painless gastro-duodenal hemorrhages aside from peptic ulcer. For this reason, we have reviewed all cases of painless gastro-duodenal hemorrhages that have come to autopsy in this hospital during the past 15 years, and those in which a sufficient resection was done to permit an anatomic diagnosis. We have

omitted cases where simple exploration was performed because exploration, no matter how painstaking, is a notoriously uncertain guide in respect to the discovery of a bleeding lesion. Cases with a loss only of occult blood have been excluded; only those that presented a considerable hematemesis or melena, associated with an appreciable anemia and clinical symptoms of hemorrhage (dizziness, fainting, fall in blood pressure), have been accepted. Moreover, lesions of the jejunum, ileum and colon have not been considered.

There were left a total of 14 cases. A brief report of each follows.

Case Abstracts. Case 1 (Path. 6253). Female, aged 68. Fever, chills and prostration 2 weeks. On one occasion had blood in stool. *Clinical diagnosis:* sepsis, perinephric abscess and pyelonephritis; right ureter obstructed. Operation: pyelotomy. On 7th day patient vomited. Gastric lavage showed old blood.

Autopsy. Purulent pyelonephritis. Thrombophlebitis of renal vein extending into inferior vena cava. Multiple emboli of branches of pulmonary artery with multiple hemorrhagic infarcts. Emphysema. Chronic mitral disease. Multiple erosions of the stomach with old blood in the lumen.

Summary. A case of sepsis following renal infection. The painless hematemesis arose from multiple erosions of the stomach.

Case 2 (Path. 7583). Male, aged 46. A case of familial hereditary telangiectasis. Umbilical pain after meals. Aspiration of stomach showed old blood. Four years later an enlarged spleen and gastric retention of blood. On last admission, history of dizziness, faintness and black stools dating 3 days previously.

Autopsy. Chronic thrombotic obliteration of portal, splenic, mesenteric and left renal veins. Multiple peritoneal adhesions. Dilation of esophageal and gastric veins; healed ulcer of duodenum.

Summary. A case of multiple hereditary telangiectasis; healed ulcer of duodenum; portal obstruction of unknown etiology. The painless melena is due to portal obstruction.

Case 3 (Path. 5951). Female, aged 24. History of probable gastric neoplasm. A few days before death, severe hematemesis is followed by severe anemia.

Autopsy. Generalized lymphosarcomatosis, hemorrhage arose from ulceration of a gastric tumor.

Summary. Lymphosarcoma; hematemesis from a gastric tumor.

Case 4 (Path. 6516). Case of aplastic anemia with purpura; hemorrhages from nose and throat; hematemesis.

Autopsy. Aplastic anemia; hemorrhages in kidney, stomach, lung and endocardium.

Summary. Aplastic anemia.

Case 5 (Path. 6720). Male, aged 48. Seven years belching and regurgitation of food; no pain. Two years occasional attacks of dizziness; 6 weeks attacks of dizziness, increasing pallor, weakness. Hemoglobin 32%; stools guaiac positive, 4+. Transfusion of 500 cc. of blood. Roentgen ray revealed an irregular bulb and a small pocket on the greater curvature of the duodenal bulb near the base. Partial gastrectomy. Resected specimen showed an ulcer on the superior wall of the first portion of the duodenum; gastritis with 6 erosions varying from 4 to 10 mm. in size not involving the submucosa.

Summary. Bleeding arose from ulcer of duodenum, gastritis and erosions.

CASE 6 (Path. 7101). Male, aged 37. Swollen abdomen 2½ months. Enlarged liver, jaundice, cholemia. On day of death, hematemesis.

Autopsy. Endophlebitis obliterans of hepatic veins, gastric erosions.

CASE 7 (Path. 7132). Female, aged 64. History of spells of vomiting for years. Following operation for cataract, developed uncontrollable vomiting with dehydration, azotemia and acidosis. Vomited large amount of bright red blood.

Autopsy. Pyonephrosis; healed duodenal ulcer; neoplasm of sigmoid.

Summary. Cause of bleeding?

CASE 8 (Path. 8258). Male, aged 50. Twelve years ago and again 3 years later hematemesis and melena with fainting. Well up to 3 days ago when there was sudden onset of melena and fainting. Hemoglobin 34%, despite several transfusions. On day of death, fainting, shock.

Autopsy. Multiple fresh erosions and hyperplastic gastritis. Healed peptic ulcer.

Summary. Healed peptic ulcer; gastro-intestinal hemorrhage from fresh gastric erosions and gastritis.

CASE 9 (Path. 8993). Male, aged 60. Anorexia, dizziness 3 days; hematemesis of a pint of blood and clots, later another large hematemesis. Blood pressure 80—50. Liver and spleen not palpable; died in coma.

Autopsy. Laennec's cirrhosis.

Summary. Hematemesis due to Laennec's cirrhosis of the liver with rupture of an esophogeal varix.

CASE 10 (Path. 9761). Male, aged 59. Two years ago, marsupialization of pseudocyst of pancreas. Vomited black liquid 10 days ago. Blood pressure 80—60; severe anemia; 3 transfusions. Signs of myocardial failure and marked cyanosis; thrombosed veins of legs. Electrocardiogram showed poor myocardial function.

Autopsy. Chronic peptic ulcer of first portion of duodenum; severe coronary sclerosis; myomalacia of left ventricle; chronic esophagitis and gastritis at cardio-esophogeal junction.

Summary. Painless gastro-intestinal hemorrhage from chronic peptic ulcer of duodenum; coronary sclerosis, and myomalacia of left ventricle.

CASE 11 (Path. 5477). In 1927, attack of abdominal cramps followed by melena. Remained well on dairy diet for 1½ years. Five hours before admission to the hospital had nausea, weakness, faintness and hematemesis of 2 full cups of blood. Hemoglobin slowly came down to 66%. Roentgen ray showed irregular contraction at midportion of duodenum. One week later partial gastrectomy. Duodenum shows very small areas of denuded mucous membrane with moderate infiltration of neutrophils and eosinophils and histiocytes with beginning fibrosis; moderate infiltration with mononuclear cells around Brunner glands.

Diagnosis. Duodenitis; probable healed ulcer. Five years later the patient feels perfectly well.

Summary. Painless gastro-intestinal hemorrhage from small duodenal ulcer.

CASE 12 (Path. 66848). Male, aged 21. Family history reveals one brother had a perforated duodenal ulcer; the other brother had "duodenal ulcer with bleeding." One week ago had melena followed by pallor and asthenia. Roentgen ray shows only an irritable bulb. Four years later reports to hospital that he has had 6 attacks of melena. Hemoglobin 68%. At this time Roentgen ray shows irregular deformity of duodenal bulb. Operation, 1 month later, partial gastrectomy; no ulcer found.

Pathologic Diagnosis. Chronic gastro-duodenitis.

Summary. Repeated melena without pain; no ulcer, only gastro-duodenitis.

CASE 13 (Path. 32749). Male, aged 37. In 1926, hematemesis 5 days before admission. Hemoglobin 25%, with 2 transfusions rose to 46%.

Roentgen ray negative. Partial gastrectomy; 2 small superficial erosions in resected portions of stomach. Ten years later, patient perfectly well.

Summary. Melena from gastric erosions.

CASE 14 (Path. 263625). Male, aged 55. In 1926, patient admitted with a history of intermittent attacks of vomiting of coffee-ground material associated with tarry stools, followed by weakness; no pain. Roentgen ray performed at another hospital 1 year previously revealed "ulcer." Roentgen ray soon after admission showed irregular duodenal bulb. Partial gastrectomy showed chronic duodenal ulcer. Fourteen years later, patient is well.

Summary. Painless duodenal ulcer with melena and hematemesis.

Classifying these 14 cases of painless gastro-intestinal hemorrhage, we find the following as causes of the hemorrhages:

TABLE 1.—CAUSES OF THE GASTRO-DUODENAL HEMORRHAGE.

1. Chronic peptic ulcer—3 cases.
2. Gastro-duodenal erosions—2 cases.
3. Erosions with healed peptic ulcer—2 cases.
4. Gastro-duodenitis—1 case.
5. Healed duodenal ulcer, no cause for bleeding found—1 case.
6. Thrombosis of portal vein—1 case.
7. Cirrhosis of liver—1 case.
8. Lymphosarcomatosis of stomach—1 case.
9. Aplastic anemia with purpura—1 case.
10. Endophlebitis of hepatic veins and erosions—1 case.

These proportions are by no means accurate as far as the incidence of painless gastro-duodenal hemorrhage is concerned, as these cases represent only patients who have been admitted to the surgical wards.

There were 5 cases of gastro-duodenal erosions, 2 in association with healed peptic ulcer and 2 without, and 1 associated with endophlebitis of the hepatic veins. If we include the case of gastro-duodenitis without erosion, we find that gastro-duodenitis with or without erosions is by far the most common cause of painless gastro-duodenal bleeding in our series. By an erosion, we refer to a loss of mucous membrane with necrosis and infiltration of the mucosa with neurophils and histiocytes. Healing, as a rule, leaves no scar. The erosion does not penetrate through the submucosa. An erosion corresponds to what is sometimes termed "acute peptic ulcer" or "Dieulafoy's ulcer." It is practically always associated with a gastritis or a duodenitis, or both.

The genetic relation of peptic erosions to true peptic ulcers is at present a much debated matter, aroused by Konjetsny's[9] views, who holds that the genesis of ulcer is a gastritis or a duodenitis with the secondary formation of erosions.

The frequent anatomic association of erosions and peptic ulcer certainly suggests such a sequence. On the other hand, such a relation cannot be accepted unreservedly, and for the following reasons:

1. We have taken particular pains to note that in most patients who have the clinical earmarks of an erosion with painless melena

or hematemesis, the characteristic psyche which precedes the onset of the ulcer for many years is entirely missing. One of us (Moschcowitz[11] has described this type previously. Briefly, patients with peptic ulcer are intolerant, aggressive, "all or nothing" folk who have strong leanings to masochism and sadism. On the contrary, patients with clinical evidences of erosion are often calm, placid and phlegmatic. Nor have they the physical constitution of patients with peptic ulcer, as described by Draper.[4] They have not the "lean and hungry" look of Cassius, the wide angled jaws, the prominent masseters and facial lines, the hard and tense expression, or the tendency to erythremia. The importance of constitution in the genesis of peptic ulcer is steadily gaining in recognition so that at present peptic ulcer is viewed by many students of the problem as a true psychosomatic disease. Indeed, we regard the determination or absence of this constitution as a vital link in the diagnosis of suspected ulcer.

2. Erosions are frequently found at autopsy as surprise findings, unassociated with ulcer and without having given rise to the slightest clinical phenomena. Such erosions are especially observed in prolonged sepsis. The possibility that, given time, such erosions may eventually develop into ulcer cannot be excluded.

3. Experimentally, erosions can be produced, though with difficulty, by ligation or by embolization of the gastric vessels. Furthermore, erosions are seen not uncommonly in the human stomach, accompanied by local arteriosclerosis. These erosions invariably heal within a short time without ever giving rise to the characteristic callous ulcer. Indeed, if it is eventually proven that an erosion becomes an ulcer, then the major problem is to discover the cause for the chronicity. Various investigators have succeeded in producing a chronic ulcer but by means that do not obtain in the human organism; for instance, by injecting chemicals in the neighborhood of the experimental ulcer, by repeated Roentgen ray applications, and so on.

Recently, Penner and Bernheim[13a,b,c] have made significant observations that throw light upon the genesis of certain types of gastrointestinal erosions. The not uncommon autopsy findings of postoperative ulcerative and membranous enterocolitis led Penner and Bernheim to investigate the cause of these lesions. In reviewing the histories of 20 such cases in this hospital, they found that invariably death was preceded by the clinical picture of shock. In a later publication[13b] they report 4 cases of acute ulcerative lesions of the esophagus and stomach which appeared post-operatively or subsequent to diabetic acidosis. In both the intestinal and gastric lesions, the changes are the same. "The earliest changes are observed in the mucosa where vascular congestion and subsequent focal hemorrhage, initially more prominent toward the base of the glands near the muscularis mucosa, are seen. Widening of the interglandular

stroma is observed, and the presence of mucosal edema. Focal mucosa necroses appear, unaccompanied by any significant cellular reaction. More extensive necroses may penetrate the deeper layers of the wall and be accompanied by an inflammatory cellular reaction. With the early or superficial lesions, the submucosa, muscularis and serosal layer may be without recognizable changes." They ascribe these lesions to the vaso-constriction conventionally recognized as the result of shock. Penner and Bernheim[13a,b,c] submit experimental substantiation of this hypothesis by the reproduction of identical lesions in the gastro-intestinal tract in various animals by repeated intraperitoneal injections of adrenalin which caused prolonged shock.

Penner and Bernheim believe that their observations explain the cases reported by Eiselsberg[5] of post-operative gastro-duodenal bleeding, which he believed was due to retrograde embolism; the majority of the cases reported by Cushing[2] of gastric erosions, which he ascribed as neurogenic in origin due to lesions of the interbrain or its various pathways; and the acute erosions of the stomach and duodenum occasionally noted in severe burns and prolonged exposure to cold.

It would be hazardous to apply Penner and Bernheim's observations to the genesis of all gastro-duodenal erosions. Clinically, certainly, shock follows and does not precede the onset of uncomplicated erosions in our reported series. The solution of the problem hangs upon whether prolonged vaso-constriction in the intestinal tract may be the result of another mechanism beside shock. In any event, Penner and Bernheim's investigation may help to explain the association of erosions with bleeding peptic ulcers in our series.

Even if eventually accepted, Konjetsny's views concerning the pathogenesis of peptic ulcer explain only part of the mechanism but they by no means explain the primary etiology of peptic ulcer, for the reason that the cause of the gastritis or duodenitis still awaits a satisfactory solution. Konjetsny's belief that the gastro-duodenitis is the result of a toxic or infectious process has not received general acceptance; certainly it is not in accord with the known constitutional and neurogenic background of peptic ulcer, nor to its distinctive localization, the incidence of the disease in regard to sex and age, and the tendency to recurrence.

Of course it is conceivable that a true peptic ulcer with all its potentialities as a focus of infection may, in some instances, give rise to a gastro-duodenitis and thus pave the way for an erosion. Witness, for instance, the not uncommon association of ulcerating gastric carcinoma and erosion. In other words, an erosion of the stomach may be the result as well as the precursor of a peptic ulcer.

All in all, in the light of our current knowledge, it is impossible to insist upon a unitary etiology and biology of gastro-duodenal erosion and its genetic relation to callous peptic ulcer. A splendid

opportunity for such an investigation is offered by repeated gastroscopy in a suitable patient. As far as we are aware, the complete life cycle of a peptic ulcer has not yet been demonstrated by a gastroscopy.

Clinically, we can assert that erosions may have a different clinical picture and course from that of the callous peptic ulcer.

Two of the painless gastro-duodenal hemorrhages in our series were caused by chronic peptic ulcer. Eusterman[6] reports that hemorrhage was the sole symptom of benign or inflammatory lesions of the duodenum in 1.5% of 1089 cases. The reason why some peptic ulcers are painless is not clear. Crohn[1] believes that the absence of pain is due to lack of sensitivity. In his patients with peptic ulcer, complicated by hemorrhage, employing the Libman test, he found that in 40.8% the patient was insensitive as compared to 12% in normal individuals. As this test is entirely a subjective one, one need be circumspect in its interpretation. In any event, it does not account for the absence of pain in the remaining 60% of sensitive individuals. Surely, pain in peptic ulcer is conditioned by factors other than the sensitivity of the individual. While there is still no agreement as to the cause of pain in peptic ulcer, Palmer and Heinz[12] submit convincing evidence that the pain is conditioned primarily by the acid content of the stomach, and that it is not directly due to pylorospasm, gastric mobility, or increased intragastric pressure, although these factors may be contributory. The size of the lesion has no bearing. Continuous neutralization of the acid slowly desensitizes the ulcer.

In how far these factors may apply to the explanation of the frequent absence of pain in pure erosions of the stomach unassociated with peptic ulcer cannot as yet be definitely ascertained. The superficiality of the lesions in erosions may serve in part as the explanation of the absence of pain, but more detailed studies of the above factors are necessary.

The one case in our series, where no cause for the bleeding could be found although a completely healed duodenal ulcer was present is similar to that reported by Reichard.[14] A non-demonstrable cause for bleeding has been reported not infrequently. Such cases were termed by Hale-White[8] "parenchymatous bleeding." Czyhlarz,[3] Kuttner,[10] Reichard,[14] Ewald.[7] These have also been reported in cholemia (deficient prothrombin and vitamin K) and in vicarious menstruation. Dr. M. A. Kugel has told us of another case of severe painless hematemesis and melena in which a subtotal gastrectomy was performed; no cause for the hemorrhage was found in the resected specimen. Unfortunately, the record of this case is lost.

The other causes of painless gastro-duodenal hemorrhage in our series require no comment.

Conclusion. Painless gastro-duodenal bleeding is usually the result of erosions and duodenitis; less frequent are true callous peptic ulcers. In one of our 14 cases no cause could be found. In painless gastro-duodenal hemorrhage where Roentgen ray evidences of peptic ulcer are absent or inconclusive, further study of the patient is obligatory to determine the cause of the bleeding. The genetic relation of gastro-duodenal erosions to peptic ulcer is discussed. In the light of our current knowledge it is impossible to insist upon a unitary origin of gastric erosion or upon its invariable genetic relation to callous peptic ulcer.

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AN APPRAISAL OF THE MEDICAL VERSUS THE SURGICAL TREATMENT OF IDIOPATHIC ULCERATIVE COLITIS.

FOLLOW-UP DATA ON FIFTY CASES.*

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ULCERATIVE colitis presents a number of fundamental problems that are as yet unsolved. The wide variety of therapeutic measures now employed in this disease and the frequency of unsatisfactory results attest to the present deficiencies in our knowledge. Opinion is divided first on the question of the specific bacterial nature of the disease. Those who deny a known bacterial etiology also doubt the efficacy of so-called specific vaccines and sera, and rely solely on a number of non-specific therapeutic measures. The second division of opinion concerns the place of surgery in treatment of the disease.

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The position taken in this matter depends in large measure upon one's opinion of the efficacy of non-surgical measures. For example, in the Mayo Clinic since the advent of "specific" therapy the number of cases treated surgically has progressively declined from 20% in the period from 1919–1923 to 1.4% in the period from 1932–1936.[2] On the other hand, those who have had less favorable experience with medical treatment employ ileostomy and analogous procedures in as high as 65% of patients with the disease.[7] Such divergence of opinion emphasizes the need of obtaining all possible data that bear on this controversial question. The present study, therefore, was made to determine whether medical treatment alone was superior to combined medical and surgical therapy in a group of patients with ulcerative colitis observed during the past 12 years in this hospital. The follow-up analysis indicates clearly that those patients in whom one of various side-tracking operations was carried out are in better physical condition and lead more nearly normal lives than those treated medically.

Method of Study. Two groups of patients have been selected from ward* and private practice. One group, 23 in number, consists of those treated by medical measures only; the other group of 27 were first treated by the usual medical measures and subsequently by one of various surgical procedures. Only the more severely ill patients, with protracted diarrhea, melena, fever and anemia are included in the medical group, while those with milder forms of the disease which are known to improve spontaneously, are excluded from the study. This was done in an effort to make the two groups as comparable as possible. Even so, those treated surgically taken as a whole, were more seriously ill, for surgery usually was employed only as a last resort. In other respects, however, such as age, sex, duration of illness and geographical location, the two groups are comparable. Seventy-five per cent of the patients were personally known to one or both of us. The diagnosis in every case was made after thorough clinical study which included repeated proctoscopic examination, at which time cultures were obtained from typical ulcers, microscopic and bacteriologic study of the stools and Roentgen examination after a barium enema. Evaluation of the results of therapy was determined after personal interviews and examinations, or, when this was impossible, by means of questionnaires sent to the patients and by communication with physicians now in charge of them. In two instances interviews were made by a hospital social service worker. In every case certain specific questions were answered, so that the data are uniform in content. Without exception the information obtained was considered by us to be adequate to permit an accurate evaluation of the patient's status.

Results. *The Medical Group.* This group consisted of 23 individuals, of whom 14 survived, 8 died of the disease and 1 of unrelated causes, giving a mortality of 34%. The 14 survivors included 5 men and 9 women. In these observations, made from 1 to 12 years after the final discharge from this hospital, an effort was made to obtain both subjective and objective evidence of their subsequent physical status. A clear picture of the usual course of the disease and the

* We are indebted to Drs. E. L. Eliason and I. S. Ravdin for the privilege of studying patients treated on their surgical services.

ultimate prognosis for the average patient treated solely by medical measures is the first requisite in deciding for or against surgical treatment.

Twelve patients, 85% of those who survived, had had diarrhea either continually (5 cases) or intermittently (7 cases) since the illness had begun, on the average, 6 years earlier. Blood repeatedly appeared in the stools of two-thirds of the group, pus in one-quarter and mucus in three-quarters. They had on the average 6 bowel movements daily (1 to 14). Only 2 patients were free of symptoms of colitis, one of whom was a total invalid because of a complicating generalized arthritis. Although the group averaged 28 pounds above the minimum weight during their illness they were approximately 10% below their usual weight. One-half of them had had to return to hospitals because of recurrences of the disease. Three were complete invalids who should have been in hospitals. All were under constant medical supervision.

It seemed to us important to learn the opinion that each patient had concerning his own health. To the question "Do you consider yourself cured of the disease?" they unanimously gave a negative reply. Not one considered himself in excellent health, only 1 regarded her health as good, 9 as fair, 1 as poor, and 3 were invalids. With respect to productiveness, 5 were totally unable to do any kind of work, 5 were capable of light work, and 4 could do medium-heavy work during remissions of the disease. All were therefore either partially or wholly dependent financially.

Of the 8 fatal cases, 4 died after discharge from the hospital. While exact details of the immediate causes of death are not available, it is known that all had continuation of symptoms and ultimately died as a result of ulcerative colitis. The remaining 4 patients died in the hospital, 1 had extensive amyloid disease and died of renal failure, 2 developed perforation of the colon with peritonitis, and 1 with hypoproteinemic edema and anemia died suddenly at night without known cause.

Surgical Group. This consisted of 27 individuals, 14 males and 13 females. Seven of the group died, giving a mortality of 26%. The causes of death, which are discussed later, were as follows: 2 cases developed high intestinal obstruction and 1 adynamic ileus early in the post-operative period, 1 man committed suicide 3 weeks after operation, another made a highly satisfactory response to ileostomy but developed multiple liver abscess 2 years later. One man died in a state of severe malnutrition, hypochloremia and dehydration soon after ileostomy. In the final case, death occurred in another hospital following repair of a prolapsed ileum.

Ileostomy alone was performed in 12 instances, ileostomy with partial colectomy in 9, colostomy in 4, appendicostomy in 1, ileocolostomy in 1. The technical surgical aspects of 17 out of 20 cases are regarded as satisfactory. Three were, in our opinion,

inadequately treated by appendicostomy, cecostomy and sigmoidostomy which failed to divert the fecal current. The results in these instances, while not satisfactory, are nevertheless included in the consideration of the group as a whole.

Without exception the 20 patients who survived operation are greatly improved in health. The average gain in weight following operation was 38.5 pounds, the greatest gain was 100 pounds, the least 15 pounds. In no case did fever continue except in the 3 inadequately treated, in whom the disease recurred, with intermittent fever and melena. The red blood cell counts uniformly returned toward or actually to normal. Seventy per cent of the entire group led what they themselves described as a normal life, indicating that the limitations imposed by the operative fecal fistula did not constitute a significant handicap. Violent physical exertion was not possible, but mild athletic exercise was entirely feasible. One man was able to resume his occupation as a construction engineer, operating a hoisting crane.

Thirty per cent of the group were not able to return to an entirely normal life. Three laborers were unable to resume their previous occupations which involved heavy lifting and other strenuous exercise. Their disability was attributable to the nature of their occupations rather than to their physical condition, which was good enough to permit light work. Two others of the group, who were inadequately treated in one instance by appendicostomy and in the other by sigmoidostomy for a ruptured colon with a pelvic abscess, did not make complete recoveries. This must be ascribed to the inadequacy of the operations rather than to failure of surgical treatment. One woman, with coincident pulmonary tuberculosis, led a restricted life on that account although she had made great improvement following ileostomy. We believe it fair, in summarizing this group of 6 patients, to say that every one was definitely improved following operation and that failure to return to an entirely normal life was due either to inadequate surgical treatment or to circumstances unrelated to treatment.

We desired to obtain the patients' own opinion of the results of operation, for in advising surgical treatment the physician must consider the possibility of serious psychologic damage by an operation which may profoundly alter one's outlook on life. We were therefore especially interested in the answers to three questions. "Do you consider your present health better or worse than it was before operation?" The reply was unanimous, every patient considered his health improved. "Do you consider yourself better off with an artificial opening than you were without it?" All but one replied in the affirmative, that is, an artificial opening was not considered too high a price to pay for the improvement in health which resulted. "If you had to make the decision again would you be in favor of or against operation?" Eighteen out of 20 answered in

the affirmative, the remaining 2 expressed certain qualifications. The most decided were those of a 20-year-old single girl who, though she felt that operation had saved her life, regarded as intolerable the inconveniences, embarrassment and restrictions which it imposed upon her, and was flatly of the opinion that life would be unbearable with a permanent ileostomy. Hers was the only case in which the ileostomy fortunately proved to be temporary. She is now in normal health. Her objections are not, therefore, to the final result, but to the means of bringing it about. One other patient who had not improved following appendicostomy was doubtful of its efficacy. This is entirely understandable, since this inadequate procedure had resulted in most of the disadvantages and none of the benefits of surgical treatment.

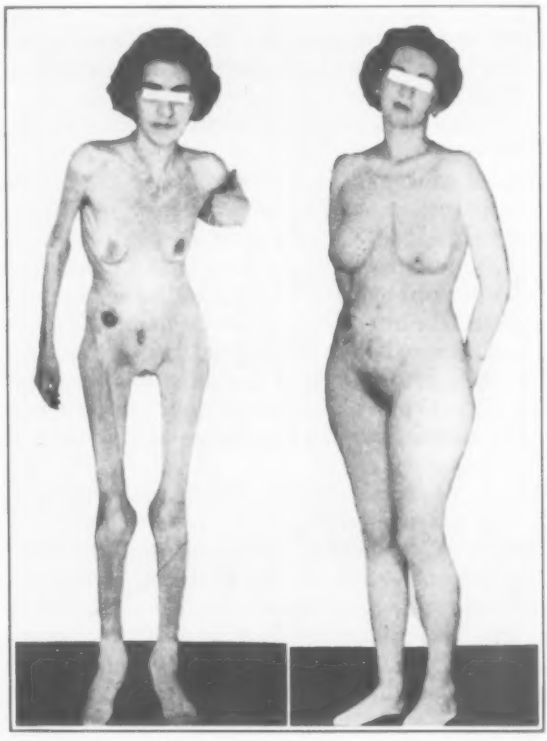
Of the 7 individuals who died only 3 had had time to gain a definite opinion of the results of operation. One was entirely satisfied, he had resumed his work and for 2 years, before the development of avoidable complications, had been completely rehabilitated. Another committed suicide 3 weeks after ileostomy. While he was definitely psychotic it must be presumed that dissatisfaction with his operation precipitated his suicide. A third man, also a psychiatric problem, definitely improved in health for 5 years after ileostomy, but regarded it as a failure. He ultimately died after surgical repair of a hernia of the ileum because of his refusal to eat. Thus, of the 23 patients who expressed opinions, 19 were entirely satisfied, 2 were partially and 2 wholly dissatisfied with the results of surgical treatment.

The discussion of certain details of surgical treatment should be prefaced by the statement that we share the opinion of Cave and Mackie,[5] Cattell[3] and others that the operation of choice is one which produces complete diversion of the fecal current at a point just proximal to the diseased portion of the bowel. In the great majority of instances this has required an ileostomy. At a subsequent time, depending upon the patient's response to the preliminary procedure, removal of the diseased colon, preferably in 3 stages, should be carried out. This general plan has been deviated from in certain instances. For example, 6 patients who had an ileostomy and nothing more have made dramatic recoveries and have maintained good health for an average of practically 3 years. Under these circumstances we think it justifiable to withhold colectomy until clear-cut indications for it appear, with the understanding that if good health does not continue operation is advisable.

In 9 cases partial or complete colectomy followed ileostomy for the various reasons: 4 did not make what we regarded as satisfactory recovery after the preliminary operation, another had serious and repeated hemorrhages from the colon, necessitating its removal, 2 developed generalized arthritis which disappeared promptly after colectomy, 1 had a carcinoma of the colon which was removed during

the original operation. In general, we believe colectomy clearly indicated unless ileostomy results in complete return to normal health, with disappearance of bloody or purulent rectal discharges, and all systemic signs of infection such as fever and leukocytosis.

It is wholly unjustifiable, in the light of both our experience and that of others to regard any side-tracking operation in this disease as a temporary measure carrying with it a reasonable expectation that the normal fecal current may ultimately be reëstablished. As



A *B*

FIG. 1.—*A*, Patient E. L. 3 weeks after ileostomy and partial colectomy. *B*, The same patient 1 year later.

mentioned earlier, in only one instance in our series was it possible surgically to close the ileostomy. The success in this case depended upon the fact that the atypical, segmental disease process, restricted chiefly to the transverse colon, cleared up in a year after ileostomy, leaving the rest of the colon essentially undamaged. After partial closure of the stoma the colon returned to its normal configuration and caliber, judged by Roentgen examination, and 2 months later, in the absence of any signs of recurring disease of the colon, complete closure of the ileostomy was possible. The patient

has remained in entirely normal health for 10 months following this procedure. However, this fortunate outcome is so exceptional that it does not constitute grounds for offering what, in the great majority of cases, will prove a false hope which only delays the successful readjustment of the patient to a sometimes difficult situation.

Complications. It is not surprising that the post-operative complications were high in a group of patients in desperately bad condition before operation. The existence of multiple vitamin deficiencies accompanied by severe anorexia made proper caloric intake difficult. Anemia and hypoproteinemic edema frequently were complicating factors. Wound healing was often slow and unsatisfactory, and wound infections were common. Decubitus ulcers were difficult to avoid. A localized pelvic abscess required drainage in one instance. Femoral thrombophlebitis occurred several times. Partial intestinal obstruction complicated convalescence in 3 instances, being relieved in 2 cases by medical measures, including small intestinal intubation, and in the third by rupture of the bowel with spontaneous formation of a fecal fistula which subsequently closed. Adynamic ileus was a terminal development in 2 of the fatal cases. We have observed, as have others,[5,6] the excessive loss of fluid and chlorides through the ileostomy discharges in the first days following operation. Unless this danger is recognized, marked hypochloremia and dehydration may quickly develop, but they are easily avoided by saline infusions and blood transfusions in the early days of convalescence. Prolapse of the ileum was a frequent late complication of operation. It occurred in 5 out of 20 cases and required surgical repair in 3 instances.

Analysis of Fatalities. Examination of the factors responsible for the fatal outcome in 4 of the 7 patients treated surgically reveals certain features which deserve consideration.

Clinical Abstracts. Case 1.—I. P. made a highly satisfactory recovery following ileostomy, gaining 76 pounds. Gradual spontaneous closure of the ileostomy 2 years later necessitated re-operation, which was again followed by a gain of 40 pounds and marked clinical improvement. In the following year arthritis developed. A year later fever and jaundice occurred, an hepatic abscess was drained. Death occurred in 3 months and autopsy revealed multiple liver abscesses, peritonitis and bronchopenumonia. The spontaneous closure of the ileostomy could have been avoided by performing complete transection of the ileum with implantation of the proximal portion in the abdominal wall. We regard this as the operation of choice. The development of arthritis and liver abscess probably resulted from the serious infection of the colon. The fatal outcome could, in all likelihood, have been avoided by timely colectomy after the preliminary ileostomy.

Case 2.—M.H. died with intestinal obstruction and toxic jaundice 5 days after ileostomy and almost complete colectomy in one stage. The fatal outcome is attributed to the fact that the primary operation was too extensive. It emphasizes the belief that the ideal procedure is preliminary ileostomy, with delay of subsequent colectomy until the patient's condition is sufficiently improved to withstand it.

Case 3.—J.B. was suffering from a fulminating type of the disease. Operation was postponed until it was apparent that death would ensue

without it. The fatality occurred soon after the second stage of the ileostomy from paralytic ileus, dehydration and general sepsis. While the operative mortality is, at best, very high in this type of ulcerative colitis, it is further increased by an unnecessary delay in surgical treatment, and can be reduced only by the closest possible coöperation between medical and surgical attendants.

CASE 4.—I.R. died 1 month after ileostomy in a severe state of malnutrition and hypochloremia. Death was attributed to inadequate postoperative care in a patient who was refractory and uncoöperative. The outcome emphasizes the necessity of constant and patient attention to details of maintenance of proper nutrition, fluid balance and routine nursing care under even the most trying conditions.

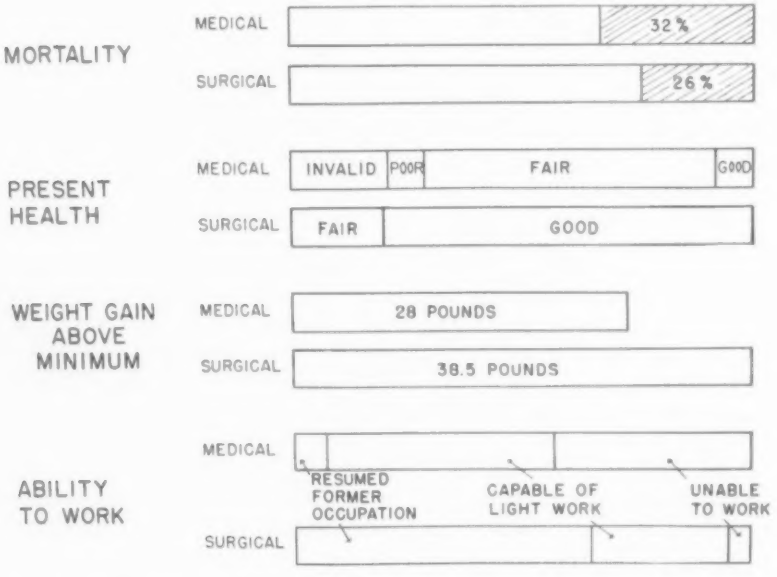


FIG. 2.—Comparative data on the present status of the medically *versus* the surgically treated patients.

Discussion. These results (Fig. 2), in our opinion, clearly indicate the superiority of surgical treatment in cases of severe ulcerative colitis. We recognize, however, that others do not share our enthusiasm: some,[1] because of greater success with medical therapy, and some,[9] because of a less favorable experience with surgical treatment. Such a difference of opinion naturally inclines us to subject our own data to doubly critical examination in an effort to discover either erroneous interpretations of the data or factors which might have favorably influenced the results of treatment in one group. We have found nothing to suggest that the surgical cases received preferential treatment in their routine care. Our cases were selected from 3 different services of the hospital, and were under the supervision of a large number of physicians holding varied opinions concerning the ideal method of treatment so that no preference of our

own for or against surgical therapy could, we believe, have influenced the results. The study has extended over a period of 12 years, sufficiently long to give accurate indication of the results of both non-surgical and surgical methods. If errors in interpretation of the data exist we believe that they have resulted in understatement of the success of surgical treatment rather than the reverse. This is true for two reasons, first, because all patients operated on were included in the study whether, in our opinion, adequately or inadequately treated, and also because of the fact that these cases by and large were far more seriously ill than even the most severe cases in the medical group.

A comparison of the surgical results in the first versus the second 6-year period of the study cannot easily be reduced to figures. However, the inadequate operations which gave unsatisfactory results were all done during the earlier period. It is our definite impression that a steady improvement in surgical treatment has occurred, which encourages us to believe that with continued experience present difficulties will ultimately be overcome.

The indications for operation may be regarded as either obligatory or optional. In the former category we include perforation of the colon, those with a fulminating type of the disease, and those who develop complications such as generalized arthritis, repeated hemorrhages from the colon and severe perirectal infection. Little difference of opinion exists here. In the other group, however, in which operation is elective, wide divergence of opinion is expressed. We regard any patient with intractable symptoms, whether intermittent or continuous, who has failed to respond to a reasonable period of medical treatment, as a candidate for surgery. What constitutes a reasonable trial of non-surgical therapy is difficult to state categorically, but our experience suggests that at present surgery is more often unjustifiably delayed than prematurely done.

The mortality rate in the two groups was essentially the same, 32% for those treated medically, 26% for those treated surgically. Since the medical group was selected to include only the more severe cases comparison to the mortality rates in the literature is difficult. The figures included in Willard's review[8] give mortality rates of from 3 to 35%. Similar figures for cases treated surgically vary from 21 to 73%.

We are in agreement with Cave,[4] McKittrick and Miller[7] and others that the most satisfactory results in the treatment of this disease are obtained by a medico-surgical team who are particularly interested in the problems concerned. The reduction in mortality which such a group can bring about has been amply demonstrated. This closer coördination of effort is especially essential in determining the nature of and optimum time for the original operation, in assuring sustained attention to the problems of nutrition while the patient is under surgical treatment, and in deciding upon the necessity for and the extent of the operations which follow preliminary ileostomy.

This disease is one, par excellence, the treatment of which cannot be regarded as primarily medical or surgical without serious detriment to the patient.

Conclusions. Two comparable groups of patients with idiopathic ulcerative colitis have been studied; one received medical treatment only, in the other various side-tracking operations were performed. The mortality in the two groups was practically equal. Comparison of the subsequent developments leads us to the conclusion that those who were operated upon were more nearly restored to normal health than those who were not. The group treated medically has had continued or intermittent manifestations of the disease and is in poor or only fair health. Those operated upon made, in most instances, dramatic recoveries. The great majority returned to their previous occupations, and lead, by their own definition, a normal life. They have expressed satisfaction with their treatment even though it has entailed a permanent external intestinal fistula.

The surgical procedure of choice is a preliminary ileostomy with subsequent colectomy in stages, if indications for it exist. We have discussed some of the causes of unsatisfactory results, the post-operative complications and have emphasized the necessity of close coöperation of internist and surgeon, if the best results are to be obtained.

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COMPLETE ROENTGEN RAY STUDIES OF THE GASTRO-INTESTINAL TRACT IN 400 ARTHRITICS.

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In a recent communication[4b] attention was directed to a variety of considerations bearing upon treatment of the arthritic and to the further fact that decreasing emphasis upon focal infection as

the chief cause of arthritis has opened the way to fuller appreciation of other influences operative both to produce the disease and to modify the course of it. The present article extends some aspects there touched upon and also continues earlier studies.

One of the present writers[4a] has previously stressed the importance of considering adequately all deviations of physiology presented by the arthritic. Among these deviations are those to be seen in the gastro-intestinal tract and some phases of this were discussed earlier, together with certain nutritional aspects, by Pemberton and Peirce.[5]

Opportunity now presents, however, for a fuller review of the field on the basis of complete roentgenographic studies of the gastro-intestinal tract in a series of 400 arthritics and 100 normals. So far as the authors are aware no survey of comparable magnitude has been previously conducted and it is reasonable to suppose that the results should indicate whether, and to what extent, the gastro-intestinal tract is implicated, from the Roentgen ray standpoint, in the syndrome of arthritis.

The series of cases studied* represents all types and stages of arthritis and had its beginning about 1920. Analysis of the gastro-intestinal tract was undertaken at that time because of the conviction of one of the authors (R.P.) that focal infection alone did not account adequately for the syndrome and that many other factors played contributory rôles. Among the last mentioned were certain clinical observations that nutritional factors, the balance of foodstuffs and the function of the gastro-intestinal tract as a whole sometimes exercise a determining influence.

Correlation of the roentgenographic data with the clinical state of the subjects is confined essentially in the present report to the two great types into which the field is generally divided; namely, atrophic (rheumatoid) arthritis and hypertrophic (osteo-)arthritis. Fuller correlation with respect to other more detailed clinical data will be made the subject of a later communication.

The usual procedure and technique for gastro-intestinal study were carried out in each case, special attention being paid to the size, position, tone and function of the various organs, as explained later in the text. In many cases findings were checked at subsequent studies and serial studies were carried out at various intervals when indicated, since the positions of organs and, to some degree, the sizes of them are variable, within normal limits, because of differences in body build.

* The earlier roentgenographic studies were conducted mostly in collaboration with Dr. William S. Newcomet, assisted at times by Dr. E. W. Spackman. Some cases were studied in collaboration with Drs. George E. Pfahler and Bernard P. Widmann. A considerable number of later studies was carried out in collaboration with Dr. J. Donald Zulick, and also with one of the present authors (E. W. S.). Obligation is herewith expressed to the above and to Dr. Newcomet and Dr. Zulick in particular for their valuable and interested coöperation.

At the outset of the present study 100 unselected complete radiographic examinations of the gastro-intestinal tract of arthritics were chosen and the findings analyzed. On the basis of this preliminary survey a detailed plan for further studies was established as shown in Table 2. This plan was then used for the quantitative analysis of the remaining 300 cases in the arthritic series. These findings were then tabulated and compared with a series of 100 normal cases selected from our services at the Presbyterian Hospital, Philadelphia. This series was reviewed to establish the criteria of normal limits, especially in regard to size and position of the various parts of the gastro-intestinal tract. In determining normal standards for this particular problem it is important to consider the build of the patient (Table 1).

TABLE 1.—ROENTGENOGRAPHIC GASTRO-INTESTINAL DATA FROM 100 NORMALS.

	Normal	*Asthenic*	*Sthenic*
A—position of lower pole of stomach	Fifth—L	4 cm. below iliac crest	Third—L
B—position of cecum	Middle third of iliac fossa	Lower third of iliac fossa	Upper third of iliac fossa
C—position of hepatic flexure	Third—L	Only slightly above crest of ilium	Second—L
D—position of splenic flexure	First—L	Second—L	Twelfth—D
E—position of sigmoid	Below first sacral segment	First sacral segment	Below first sacral segment

Upper and Lower Limits of Normal Width of Colon.

Cecum	4 to 6 cm.	Descending	3½ to 5 cm.
Ascending	4 to 6 cm.	Pelvic	3 to 5 cm.
Transverse	3½ to 6 cm.	Rectum	6 to 8 cm.

It is well recognized that the asthenic type of individual often presents features suggestive of enteroptosis, whereas the more sthenic type does so less often. Some consideration must therefore be exercised towards what is to be considered as normal for the asthenic type and, by the same token, for the sthenic type. On the other hand, given this distinction, standards of normality may still be loosely applied in evaluating Roentgen ray studies of the gastro-intestinal tract. Thus, it by no means follows that a condition of marked enteroptosis, together with redundancy and sharp angulation of the colon, encountered in a person of asthenic type, is to be regarded as wholly normal and provision was therefore made to evaluate such departures.

The normal series consisted very largely of symptom-free patients

who were referred for gastro-intestinal study as part of a general checkup examination and generally complained of nothing directly referable to the digestive system. Thirty-two of these patients were normal as to general body build, 20 were sthenic in type, and 48 were asthenic. Table 1 indicates the upper and lower limits as to size and position of the organs for all three types. The width of the various portions of the colon showed less variation due to the body build than did the position of the flexures, and the limits determined in the diameter of the colon were therefore merely upper and lower limits of normal for these measurements irrespective of the patient's build. From the analysis of the 100 normal cases the values occurring with the greatest frequency were computed and these data comprise the basis for Table 1.

TABLE 2.—RESULTS OF PRELIMINARY STUDIES ON THE GASTRO-INTESTINAL TRACT OF 100 ARTHRITICS, INDICATING POINTS TO BE NOTED IN ROUTINE STUDIES.

Esophagus:
No findings of interest in arthritics.
Stomach:
Structure—size, position, type.
Function—peristaltic activity, character of waves.
Special—tenderness, irregularities and defects, retention at 6-hour period.
Duodenum:
Structure—size, position.
Function—emptying time, tone, peristaltic activity.
Special—defects, tenderness, dilatation, irregularity or delay and other duodenal loops.
Gall bladder:
Structure—size, position and regularity of outline.
Function—absorption, concentration and fat response.
Special—tenderness, calculi, fixation, flexibility.
Small Intestines:
Structure—general pattern.
Function—distribution at the 6-hour interval, residue at the 24-hour interval, and motility.
Special—tenderness, irregularity in pattern, defects.
Colon:
Structure—size, position, haustral appearance; individual parts studied were the cecum, ascending, transverse, descending and pelvic colon, rectum and flexures.
Function—tone and motility.
Special—defects, comparative study of position of various parts in lying and standing postures, position of appendix and iliocecal valve, regurgitation.

Having estimated the criteria for normals, 300 cases of arthritis of both types were studied from the services of the writers at the Presbyterian Hospital, Philadelphia, the Abington Memorial Hospital, Abington, Pa., and from their private practices. Note was made of all variations from normal, comparing the arthritics with the normal standards, above described, but without reference to the type of arthritis, stage of the disease or any other clinical features of the case. The various features of this analysis are outlined in Table 3.

The findings in the 300 cases analyzed in this manner were tabulated and the results compared with the original 100 cases

examined at the beginning of the study. Inasmuch as close correspondence of the figures for the two groups was obtained the findings were therefore considered to be reasonably representative of arthritics as a group. Review of the data thus obtained reveals that chronic arthritis, irrespective of type, is associated with a certain set of features or deviations from the norm, revealed by Roentgen ray examination of the gastro-intestinal tract, which might almost be called an "arthritic pattern." No single feature noted is typical of rheumatoid disease but a combination of features is so constant that it can be regarded as a significant part of the general picture of chronic arthritis.

TABLE 3.—SUMMARY OF THE PRINCIPAL ABNORMALITIES ENCOUNTERED IN THE GASTRO-INTESTINAL TRACTS OF 300 ARTHRITICS.*

	No. of Cases.
Esophagus:	
No findings of importance.	
Stomach:	
Abnormalities of structure and position	92
Abnormalities of function	99
Abnormalities in special group (especially defects)	16
Duodenum:	
Abnormalities of structure	27
Abnormalities of function (especially irritability and spasm)	184
Abnormalities of special group (especially ileus)	4
Gall bladder:	
Abnormalities of structure and position	237
Abnormalities of function	281
Abnormalities in special group (especially calculi)	44
Small intestines:	
Abnormalities of structure	2
Abnormalities of function (especially in distribution of barium at the 6- and 24-hour periods)	204
Colon:	
Abnormalities of structure and position	361
Abnormalities of function (especially excessive regurgitation and abnormal retention after passing)	201
Special group (especially defects)	28

* Attention is directed to the fact that one organ such as the stomach or gall bladder may present several deviations from normal. For purposes of brevity the sum of deviations is presented, even though such a sum may suggest undue extent or frequency unless this fact is kept in mind. A detailed consideration of these deviations will be made the subject of a later communication.

The extent of deviations from normal within the gastro-intestinal tract is not necessarily, but usually, in accord with the general condition of the patient. The deviations are generally more pronounced in advanced cases and less marked in early cases. There is no distinctive aspect of any of the several features studied characteristic "*per se*" of arthritis, *e. g.*, pyloric irritability and duodenal spasticity, when present, appear in arthritis precisely as they do, when present, in gastric or duodenal ulcer, disease of the gall bladder, appendicitis and other local or systemic conditions.

Abnormalities appear in either the gall bladder, stomach or small intestine in about 60% of cases. The complex most nearly characteristic of the arthritic syndrome is seen in relation to the colon.

At least 80% of arthritic cases present deviations from normal in this region. Two general phases of gastro-intestinal tone or balance, with intermediary gradations, are to be observed; namely, atonicity and spasticity. Hypotonic manifestations of part or all of the colon occur in about 40% of the series and completely atonic manifestations in nearly 10%. Occasionally one part of the colon shows atonicity while another shows spasticity.

TABLE 4.—SUMMARY OF DATA REGARDING ABNORMALITIES IN VARIOUS ORGANS FROM THE ROENTGEN RAY STANDPOINT.

Esophagus:
No important deviations from normal appear except spasm.

Stomach:
Ptosis, dilatation, flabbiness, hypotonicity, changes in motor mechanism are frequently present (20% to 30%). Other features such as irritability, spasm, are often present but are regarded as of minor significance.

Duodenum:
Hypotonicity and irritability are commonly found (15%); fixation, tenderness, delay and organic deformities are less frequent (3% to 5%).

Gall bladder:
Ptosis, dilatation, subnormal absorption, subnormal concentration and response to fats or even non-function may appear. One or more of these departures from normal was observed in over 50% of the subjects studied. Other data have been encountered which may be considered as indicative of possible infection, past or present, such as adhesions. Calculi are sometimes found (approximately 10%).

Small intestine:
Disturbance of motor function in respect to either hyper- or hypoactivity is more commonly found than is any other feature in this region (15% to 20%).

Colon:
Cecum: Dilatation, atonicity and ptosis are the most frequent and characteristic features (80%).
Ascending colon: Dilatation, haustral irregularity, hypotonicity are common; sometimes irritability is present.
Hepatic flexure: Ptosis, hypermobility, folding and redundancy are frequently present.
Transverse colon: Ptosis, hypermobility, folding, haustral irregularity and spasms are common.
Splenic flexure: Elongation and redundancy are commonly noted.
Descending colon: Narrowing of lumen, haustral absence or irregularity, spasm, folding, sometimes associated with local tenderness or rigidity, are observed.
Sigmoid: High looping and excessively redundant type with dilatation is characteristic.
Rectum: Dilatation is common.

In order to determine whether any feature of the gastro-intestinal findings differentiates the two types of arthritis or accompanies chiefly one or the other type, 100 unselected cases were reviewed, 58 being of the atrophic variety and 42 of the hypertrophic variety. No such correlation was evident. Apparently the deviations from normal in the gastro-intestinal tract are similar in all essential respects in each variety.

Table 4 gives a summary of the main findings in the series of 400 cases under investigation.

Certain of the patients who exhibited slight clinical manifestations of arthritic activity at the time of examination presented from the gastro-intestinal standpoint a pattern comparable to that char-

acterizing severe arthritis. Some of these patients subsequently developed notable clinical activity in respect to arthritic manifestations. Whether such conditions in the gastro-intestinal tract can be regarded in any sense as predisposing factors cannot be definitely ascertained from the present study alone.

It can be fairly said, however, that in the study of arthritic cases at large, recognition of the type of variation in the radiologic field here discussed may definitely assist the clinician in estimating the extent to which a background of constitutional or structural weakness may be present in given cases. The results of the present study are not to be regarded as of diagnostic value but when obvious precipitating factors are absent, such as marked focal infection and the like, it becomes proper to give greater emphasis to the gastro-intestinal findings and to the varied implications which they bear in a systemic as well as a local sense.

Parallel with the general course of the uninfluenced disease there is a tendency for some of the deviations of the gastro-intestinal tract above described to become more marked, particularly as regards ileal stasis and the configuration of the large bowel. This tendency is recognizable as concomitant with chronic disease of several kinds and, as remarked earlier, the deviations described in the foregoing text can be in no sense regarded as confined to or pathognomonic of the arthritic syndrome. It is perhaps superfluous to add that appreciation of this last mentioned fact in no wise obviates the necessity of evaluating the above deviations and determining their significance from the etiologic, pathologic and therapeutic standpoints. It may be well, however, to point out that the influence of abscessed teeth, or an infected prostate, in precipitating arthritis is well recognized although such foci of infection are also to be found in countless persons in apparent health. Indeed, one of the difficulties characterizing some approaches to understanding and treatment of the arthritic syndrome has been an "all or none" attitude on the part of some observers. The fact that deviations of nutrition and of the gastro-intestinal tract do not explain all the phenomena of arthritis has led to a form of negation which has minimized such considerations in spite of the further fact that parallel developments in the field of nutrition at large and in the gastro-intestinal tract and the deficiency diseases in particular, testify to an intimate and delicate balance between the processes there operative. Deviations from the processes of normal nutrition, at any link of the chain, may not only be significant on their own account, alone and in combination; they may even determine the existence of an infectious process and conditions its influence. Viewed in this light apparently minor departures from normal of anatomic or physiologic nature must be accorded a potential significance far beyond the surface implications.

Thus, by way of illustration, the roentgenographic findings as

regards the colon afford explanation, and some corroboration, of studies conducted by Stabler and Pemberton[6] which revealed that the bacterial count of the feces among arthritics was definitely higher than among normals, although the kinds and proportions of organisms showed no great differences. The full significance of this correlation is not yet apparent but it is to be noted that McCarrison[3] and others have induced in the large bowel of monkeys, by diets inadequate in vitamin B, a similar picture of elongation, dilatation and redundancy. This anatomic deviation can be carried on experimentally to changes in the mucosa amounting to colitis and in such animals there is clear evidence of the passage of bacteria through the walls of the gut with involvement of lymphatic nodes. It is not to be supposed that this situation has been demonstrated in its entirety in arthritics, though in advanced cases much of the picture may be observable clinically, and volvulus or intussusception, with obstruction, has been met in several of the cases forming the basis of the present report.

Elongation and dilatation of the large bowel are referable to atonicity of the 3 so-called "muscular bands" of the colon and this is a function not only of certain avitaminoses, particularly B Complex, but also of the balance of the autonomic nervous system.

It is common knowledge to close students of arthritis that the nervous system may play an important rôle in precipitating or perpetuating the disease and that part of the accepted value of conditioned rest in the treatment of arthritics finds explanation in the influence it exerts on the nervous system. This influence is achieved partly through the removal of undue stimuli, but is reciprocal with other factors such as the dynamics of the circulation, the extent to which optimal nutrition is approached, the presence of infection, and so on. In this general connection reference should here be made to the fact, first brought out by Fletcher[1] and corroborated by Pemberton and Peirce[5] that, as arthritics showing dilatations and redundancies of the bowel undergo convalescence, striking changes in configuration and function of the bowel may occur, so that serial roentgenograms present marked contrasts, the later ones being hardly recognizable in terms of those first taken. Further evidence indicating the significance of these general findings is probably to be found in the occasional value of colonic irrigation in the treatment of selected cases of arthritis. In any event, the data at hand do not permit strong negative postulates that deviations in configuration, position and function of the colon of the extent mentioned can have no bearing upon physiologic processes with which that organ is primarily and secondarily concerned. On the contrary, the data herewith submitted indicate strongly, what clinical experience has long borne out, that arthritics as a group are accompanied by dysfunction of the gastro-intestinal tract, chiefly in the lower bowel, but also elsewhere, which is not

only susceptible of betterment but should be included in any wide-angled therapeutic approach to the problem as a whole. There is no opportunity here to discuss the measures available to this end. Suffice it that they centre around conditioned rest, equilibrium of the nervous sytem, optimal nutrition, including adjustment of the balance of the foodstuffs, the establishment of normal gastro-intestinal function and control of the influence of infection, if any.

These considerations are not to be interpreted as implying that the gastro-intestinal deviations described, when present, constitute the chief factors to which attention should, in the care of arthritics, be given. On the contrary, they may in many instances be of academic interest only. On the other hand, in some instances in the series under discussion, therapy directed at more obvious factors proved unavailing and convalescence was initiated only when the gastro-intestinal tract was made the object, directly and indirectly, of intensive care. Such well marked deviations of the gastro-intestinal tract as a sluggish, not to say obviously infected, gall bladder usually receive appropriate study and treatment. This is not so usual, however, in cases of arthritis showing minor degrees of gastric retention, hypochlorhydria, ileal or colonic stasis or enteroptosis. The incidence of hypochlorhydria has been shown by Hartung and Steinbrocker[2] to be significantly high, 17% in atrophic and 28% in hypertrophic arthritis. Achlorhydria has been found by the same investigators in 3% of atrophic and 36% of hypertrophic arthritics. Replacement therapy here may have valuable consequences. The simply achieved but graphic influence of rest in recumbency upon a ptosed stomach or redundant and folded colon may be very significant.

It is the conviction of the writers that rectification of these and other departures from normal in the gastro-intestinal tract cannot be expected to have graphic results, or indeed any consequences, unless conducted in conformity with a balanced plan of therapy which considers all aspects of the problem, beginning usually with bed rest, and coördinating from then on all measures brought to bear.

Space does not permit of enlarging here further upon the importance of this attitude towards the therapy of arthritis which has been set forth in previous communications.[4a,b,5] Whether or not the several deviations of the gastro-intestinal tract above discussed underlie the syndrome at times or are invariably consequences of it, the fullest possible rectification of them is a biological indication all too frequently ignored or overlooked. Only benefit in a wide sense can accrue from such practice and the clinical evidence is unmistakable that in certain cases of arthritis the influence of such considerations is not only contributory but even a *sine qua non* of successful therapy.

Summary. 1. Roentgenographic study of the gastro-intestinal tract has been conducted upon 400 arthritics and upon 100 control subjects. Upon the basis of data afforded by the control subjects,

reference points have been established for the various positions of parts of the tract and for limits of function.

2. Among arthritic subjects, deviations from normal structure and function have been encountered in the stomach, gall bladder, small intestine, or in some combination of these, in approximately 60% of the cases. The complex most nearly characteristic for arthritis is seen in the colon which presents ptosis, dilatation and/or atony in 80% of cases.

3. No one of the above deviations is typical of rheumatoid disorders but a combination of them constitutes a more or less definite pattern in severely ill arthritics. There is a tendency for these deviations to parallel the general condition of the patient.

4. Whether the deviations discussed underlie the syndrome or are consequences of it, rectification of them is a clinical indication.

5. The measures necessary to this end are varied and must be coördinated. Apart from care of the gastro-intestinal tract *per se* in respect to hydrochloric acid replacement, lubrication, provision of bulky food, and so on, therapeutic measures must centre around systemic rest, equilibrium of the nervous system, optimal nutrition, the control of infections, and a balanced plan of therapy which considers all aspects of the problem and of the patient.

6. Neglect of the philosophical and therapeutic considerations inherent in these findings accounts for much of the difficulty experienced in treatment of arthritics as a group.

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THE RELATION BETWEEN PLASMA AND DIETARY ASCORBIC ACID.

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Numerous experimental studies have demonstrated that in the guinea pig the ascorbic acid content of the tissues is dependent upon the amount of the vitamin administered as a supplement to the

scorbutogenic diet.[6,11,13,15,23] Similarly, in the case of human subjects, most investigators have found that the concentration of the plasma ascorbic acid reflects the level of the dietary intake,[1,3,12,14,16,21] although the quantitative aspects of this relation have not been clearly defined. In the present investigation we have sought to characterize more exactly the relation between plasma and dietary ascorbic acid levels in healthy human subjects aged 12 to 35 years who were following their usual dietary habits.

Methods. The plasma ascorbic acid concentration was determined by indophenol titration of metaphosphoric acid filtrates under conditions essentially similar to those of the macro method of Farmer and Abt.[10] Oxalated blood samples were collected from subjects in the fasting state; potassium cyanide was not used, as it has been reported to be unnecessary and to lead to error.

The estimation of the average daily intake of ascorbic acid in the diet was a more difficult matter. Our subjects followed their usual dietary habits, and, for a period of 10 to 14 days, kept a careful record of the weights of all foods consumed, using a spring balance for that purpose. We found it necessary to prepare our own conversion table for use in translating these records into terms of the average daily ascorbic acid intake. As reported elsewhere,[4] our conversion table is based on figures obtained from the literature, but is heavily weighted to favor our own analytical values for the ascorbic acid content of foods similar in respect to variety, brand, season, storage, preparation and cooking to those eaten by our subjects. Over 500 samples of prepared food were analyzed for this purpose, and the technique and possible accuracy of our estimates are discussed in the reference cited.

Only subjects free from acute or chronic medical disease were selected for this study. Their state of health was assessed by an interview in which their previous medical history was reviewed and such physical examination performed as was indicated.

In all, we are reporting 65 correlations of the plasma and dietary ascorbic acid levels of 56 individual subjects. Of these, 33 were student dietitians, medical students, or laboratory workers, while 23 were hospital out-patients free from medical disease, and obtained for the most part from the Walter G. Zoller Memorial Dental Clinic through the courtesy of Dr. James R. Blayney. The total material is divided into two groups as follows:

Group I consists of 41 correlations of the plasma and dietary ascorbic acid levels of 36 individual subjects. Of these, 22 were males and 14 females; 15 were between the ages of 12 and 19 years, while 20 were from 20 to 35 and one subject was 42 years old. In this group a plasma determination was made at the beginning and end of a 10 to 14-day weighed diet record, and only those cases included in which the two plasma determinations agreed within 0.2 mg. per 100 cc. Group I comprises our more accurate correlations.

Group II includes 24 correlations in 20 additional subjects, and is set aside from Group I either because the diet record was kept in terms of measured rather than weighed portions (a less accurate method), or because only a single plasma determination was done, and it is less certain that the subject was in equilibrium with his diet.

All subjects are included in this report except those excluded (a) because they fell outside the specified age group, 12 to 35 (42) years; (b) for reasons of health; or (c) because their two plasma determinations differed by more than 0.3 mg. per 100 cc. and equilibrium with the diet was questioned.

Results. The results of this study are presented as scatter-point diagrams (Charts 1 and 2), in which the average daily intake of

ascorbic acid per kilo of body weight is plotted against the average plasma ascorbic acid for the period studied. Chart 1 presents the 41 correlations of Group I, while Chart 2 presents all 65 correlations of both groups. Taking into account errors inherent in our method, we consider that Charts 1 and 2 satisfactorily demonstrate the close dependence of the plasma concentration on the vitamin intake per

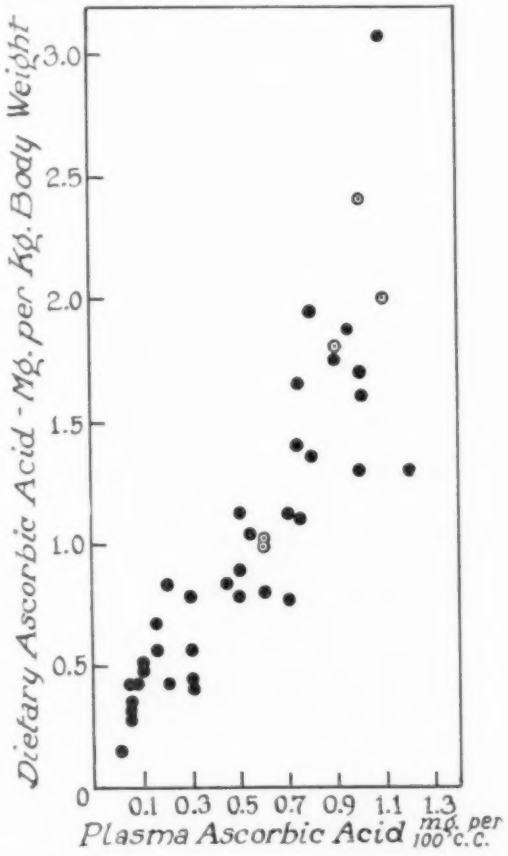

CHART 1.—Correlation of the fasting plasma ascorbic acid concentration with the average daily intake of ascorbic acid per kilo of body weight (Group I).

kilo of body weight. At least three types of error may affect the observed relation between the dietary and plasma level and hence cause undue dispersion of the points on the graph. First, it is our experience that repeated plasma determinations in a subject receiving a known, constant daily intake of the vitamin may vary by as much as 0.2 mg. per 100 cc., and the technical error of the

method is 0.1 mg. per 100 cc. Second, the value here assigned to the ascorbic acid intake is an estimate rather than a direct determination. Finally, the eating habits of many of our subjects were somewhat irregular in respect to vitamin C, and it may be questioned whether in these cases their plasma had always attained complete equilibrium with their dietary ascorbic acid.

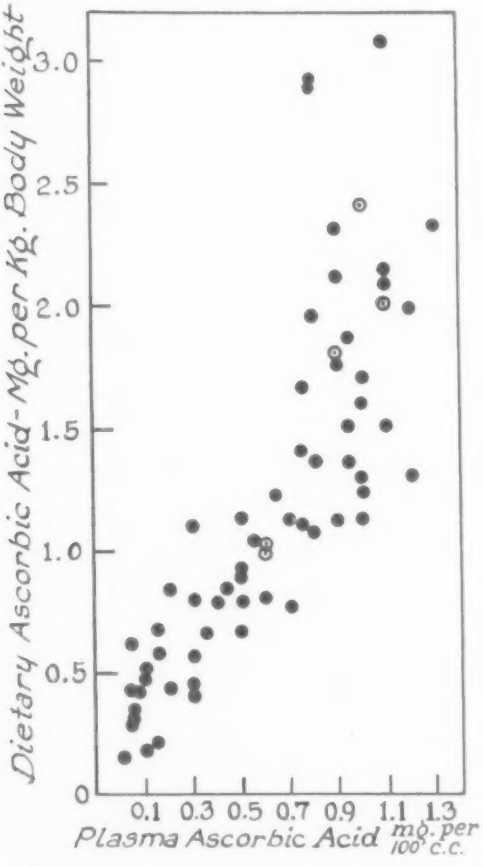

CHART 2.—Correlation of the fasting plasma ascorbic acid concentration with the average daily intake of ascorbic acid per kilo of body weight (Group I plus II).

It will be noted that we have expressed the ascorbic acid intake in terms of milligrams per kilo of body weight. If we plot instead, the total average daily intake regardless of body weight we obtain a wider scatter of experimental points than is noted in Chart 1. We have also tried plotting the relation between plasma concentration and the daily ascorbic acid intake both per square meter of body

surface and per 100 calories of calculated basal metabolism, and we find in each case a correlation which approaches more nearly that seen in the charts here published. We believe, however, that the unavoidable variability of our data makes it impossible to decide from comparisons of this sort whether or not the metabolic rate is as important as body weight in determining the requirement for ascorbic acid. Animal studies are likewise inconclusive on this point. In guinea pigs weighing from 120 to 1040 gm., Dann and Cowgill[8] found that the amount of vitamin C necessary to protect against scurvy was directly proportional to the body weight, and little, if at all, influenced by the metabolic rate. But others have shown that thyroid feeding increases the dose of vitamin necessary to protect guinea pigs against scurvy,[19] and decreases the amount of ascorbic acid to be found in their tissues.[9,17,20]

Returning to our charts, it will be noted that the plasma concentration increases in a more or less linear fashion with increasing dietary intake until the latter reaches a value in the neighborhood of 1.7 to 1.9 mg. per kg., and the plasma approximates 1.0 mg. per 100 cc. A further rise in the intake has much less effect on the plasma level. This abrupt change in the correlation between intake and plasma concentration is, of course, a reflection of the condition widely discussed in the literature under the term "saturation," in which the tissue "stores" are considered to be full, and the body responds to a large test dose of ascorbic acid by excreting in the urine a good proportion of the extra vitamin administered.

Other workers have determined by different techniques the amount of vitamin C necessary to maintain saturation in healthy adults and their results tend to confirm our findings. Ralli, Friedman and Sherry,[18] for example, found in extended studies of 3 experimental subjects that the ingestion of 100 mg. of ascorbic acid a day caused a maximum retention of the vitamin and stabilized the plasma concentration at or above 1.0 mg. per 100 cc. Although Ralli and co-workers do not consider body weight a factor, if we take the liberty of calculating intake per kilo from their report we obtain 1.4 to 1.6 mg. per kg., figures approaching those indicated in Chart 1. Also, Belser, Hauck and Storvick[2] and Todhunter and Robbins[22] found in experiments of shorter duration that saturation, as judged by the urinary response to a test dose, could be maintained by intakes of 1.2 to 1.7 mg. per kg. (7 subjects), and 1.6 to 1.7 mg. per kg. (3 subjects), respectively.

Indeed it should be possible to predict from Chart 1 the daily intake necessary to stabilize an individual at a given level of plasma ascorbic acid. To test this point the experiments presented in Table 1 were performed. The plasma concentrations of 5 normal subjects were adjusted to the levels to be tested by increasing or decreasing their vitamin C intake. Each was then given a diet practically devoid of the vitamin together with a supplement of

synthetic ascorbic acid or titrated fruit juice at each meal such that his total daily intake was that indicated in Chart 1 as necessary to maintain the new plasma level. The experiments were continued for 10 or 11 days, except for one which lasted 25 days, and in no case did the plasma value vary by more than 0.2 mg. per 100 cc. The 5 correlations of plasma and dietary ascorbic acid obtained in this way are included in Charts 1 and 2 as hollow circles in place of the solid dots which represent the other correlations.

TABLE 1.—THE DAILY INTAKE OF ASCORBIC ACID NECESSARY TO STABILIZE THE FASTING PLASMA ASCORBIC ACID AT A GIVEN LEVEL.

Subject.	Sex.	Age.	Weight, kg.	Average fasting plasma ascorbic acid, mg. per 100 cc.	Daily intake of ascorbic acid.		Duration of experiment, days.
					Total, mg.	Per kilo body wt. mg./kg.	
1	M	21	66	0.6	66	1.0	25
2	M	24	68	0.6	69	1.0	11
3	M	20	82	0.9	150	1.8	11
4	M	15	40	1.0	95	2.4	10
5	M	22	59	1.1	118	2.0	11

Discussion. The results presented in this paper indicate that in normal human subjects, 12 to 35 years of age, who are in equilibrium with their diet, the level of the plasma ascorbic acid in the fasting state is a function of the average daily intake of ascorbic acid, the latter perhaps best expressed as intake per kilo of body weight. For this reason, the determination of the fasting plasma ascorbic acid in the healthy subject provides a useful tool in nutrition studies as it helps to characterize in an objective way the subject's previous diet. Repeated plasma determinations offer an indication of whether or not an individual has attained equilibrium after a significant change in his vitamin C intake. The effect of various pathologic processes on the relation between plasma concentration and dietary intake of ascorbic acid requires further study.

It should be noted that the fasting plasma ascorbic acid runs its full gamut of change, and reaches zero, a good while before any signs of clinical scurvy can be found. Thus Crandon, Lund and Dill[7] reported that the first symptoms of scurvy appeared in their experimental subject after his plasma concentration had been zero for 120 days, and after he had been completely deprived of vitamin C for 161 days. Butler and Cushman[5] have advocated the determination of the apparent ascorbic acid content of whole blood, or of white cells plus platelets, as an index of vitamin C deficiency extending beyond the limits imposed by the disappearance of ascorbic acid from the plasma. Nevertheless, in our experience, plasma concentrations of less than 0.1 mg. per 100 cc. have been associated with very low intakes of ascorbic acid, 5 to 20 mg. a day, so that even under these circumstances the plasma determination helps to characterize the diet.

Summary. 1. In healthy human subjects, 12 to 35 years of age, who are in equilibrium with their diet, the level of the fasting plasma ascorbic acid is a function of the average daily intake of the vitamin, the latter perhaps best expressed as intake per kilo of body weight.

2. Saturation, with a plasma concentration of approximately 1.0 mg. per 100 cc., occurs with intakes in the range of 1.7 to 1.9 mg. of ascorbic acid per kilo. With lower intakes the plasma level varies directly with the intake; higher intakes cause little further increase in the plasma.

3. From the data here reported, the daily intake of ascorbic acid necessary to stabilize a normal individual at a given level of plasma concentration may be predicted.

4. Determination of the fasting plasma ascorbic acid affords a useful, objective method of characterizing the diet of the normal individual in regard to his previous vitamin C intake.

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EFFECTIVENESS OF METHYL TESTOSTERONE ADMINISTERED ORALLY.

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It has been repeatedly demonstrated that testosterone therapy, in the form of testosterone propionate, administered by injection has proved to be of definite value in the treatment of certain hypo-

gonadal states, such as eunuchs, castrates, eunuchoidism, and the like. Also, investigations and studies on inunction and implantation therapy are being made. Needless to say the most desired step now would be the evaluation of oral therapy of some form of testosterone. In 1937, Foss[2a] attempted oral administration of testosterone in a castrate of 38 years, after successful treatment by injections. Plain testosterone in dosages up to 100 mg. per day, has little or no effect on potency. As a further proof of oral inefficacy of glandular preparations, Dodds[1] concluded that all desiccated protein preparations of organs, except that of thyroid, were inactive.

In 1938, Miescher and Tschopp[3] discovered that methyl testosterone was considerably more active by mouth than any of the other preparations previously investigated, namely, testosterone, androstanediol, androstenedione, testosterone propionate, and androsterone. This was demonstrated by the increase in the weight of seminal vesicles and prostates of castrated male rats. They suggested that possibly greater protection of the active hydroxyl group from fermentative influences in the alimentary tract was acquired from the adjacent methyl group.

Foss[2b] again was among the first to try this preparation clinically. He demonstrated that it was able to maintain excellent potency in a post-pubertal eunuch with 100 mg. methyl testosterone by mouth daily, using 10 mg. tablets. Doses of 50 mg. methyl testosterone, daily, maintained fair to adequate potency. This dose was far superior to 100 mg. of plain testosterne. Excretion tests showed adequate utilization and maintenance of dose levels. Foss[2b] further tried it on hypogonadal boys, with and without obesity. The dose varied from 25 to 50 mg. per day, and he reported satisfactory results. In women, methyl testosterone was found of distinct value in some cases of dysmenorrhea. No specific toxic effects were noted aside from some slight gastric irritation, nausea, anorexia, but relieved by alkaline medication.

Having obtained a supply of methyl testosterone,* we decided to use it in several different types of cases, as follows: 1, as primary treatment in a mild eunuchoid, aged 18; 2, as a maintenance therapy in a patient with hypopituitarism associated with hypogonadism, who had already made startling progress with testosterone propionate by injection; 3, as primary treatment in a case of hypopituitarism with stunting of growth and hypogonadism; 4, as primary treatment in a 16½-year-old post-operative eunuchoid (following operation for hernia and undescended testes); and, 5, as primary treatment in a 22-year-old eunuchoid.

Case Abstracts.—Case 1. E. S., aged 18, presented himself on December 15, 1939, because of lack of supra-pubic, axillary and facial hair, small penis, high pitched voice, absence of the normal libido for this age, and no

* The methyl testosterone was supplied by Schering Corporation, through the kindness of Dr. Max Gilbert.

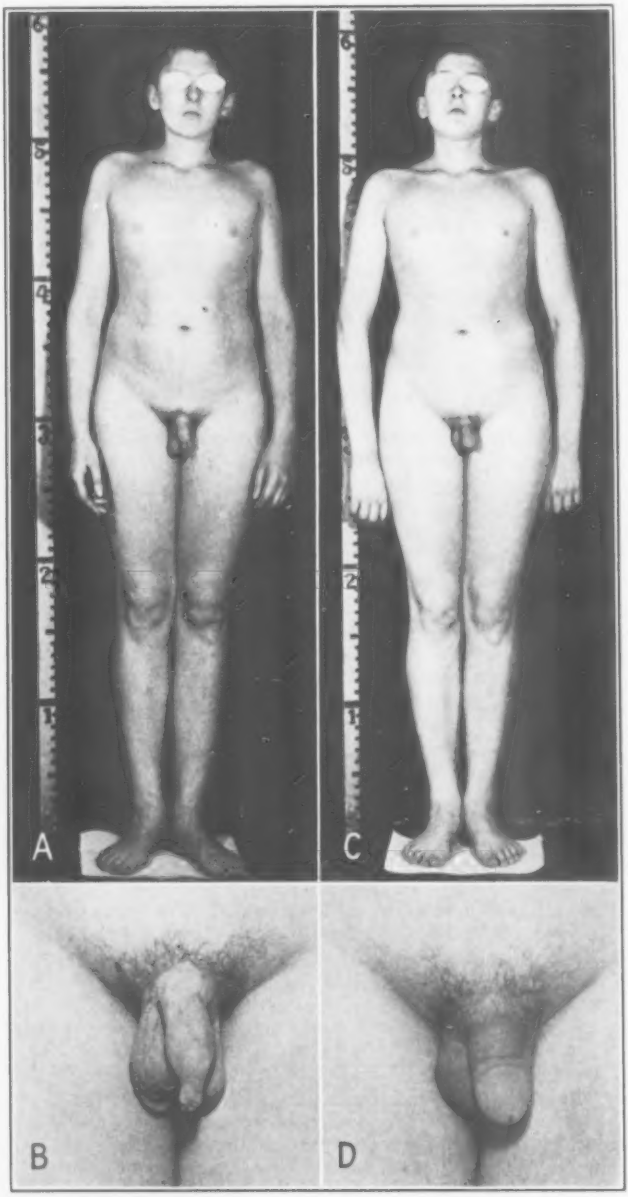
history of erections. He was 70 inches tall. Physical examination was otherwise negative. He was placed on 150 mg. methyl testosterone by mouth per day, taken as 50 mg. three times daily. Within 3 weeks there was definite enlargement of the penis, increase in supra-pubic and axillary hair, and numerous erections. Because of a phimosis, it was decided to perform a circumcision, and so the methyl testosterone was stopped after 1 month to permit a subsidence of erections and libido. With the discontinuance of therapy, there was a distinct decline in the erections, libido, hair, growth, and so on.

Case 2.—M. E., aged 14, was an example of Lorain-Levi Infantilism. Because of definite retardation in growth, treatment with growth hormone (Phyone) was commenced at the age of 8, and continued for 1 year. After a year without treatment, injections were resumed, using Antuitrin-G and Antuitrin-S. From the age of 10 to 14, treatment had been continued off and on, and his height increased from 40 inches to 48 inches, but at 14, his genitalia remained those of a child of 6. He was in the fifth term high school, bright and intelligent, had a very high pitched voice and no facial, axillary or supra-pubic hair. He had never had an erection. The testes were barely palpable, the scrotum exceedingly small. He appeared to be about 6 or 8 years of age. The physical examination was otherwise negative. Roentgen ray photographs of the wrists revealed bones somewhat small for the age, and epiphyseal development relatively normal. The sella turcica was within normal limitations, shape and size. From October 1, 1939, to December 9, 1939, he received injections of Growth Complex (Ayerst, McKenna and Harrison) 5 cc. twice weekly, and 22 injections of testosterone propionate (Oreton), 25 mg. each. The changes were so striking that they challenge description (see photographs). At this point, December 15, 1939, he was placed on 150 mg. methyl testosterone per day (50 mg. three times daily), and this was continued to May 7, 1940. The effects of testosterone as demonstrated originally by the injections were continued—growth of genitalia, growth of hair, increasing depth of pitch of voice, growth of 4 inches in height, gain of 17 pounds in weight, complete change in configuration, appearance, and so on. From May 7, 1940, to October 15, 1940, he was without treatment. There was slight regression during this period—number of erections were reduced, and the amount of supra-pubic hair was slightly decreased.

Case 3.—C. B. came under observation on September 22, 1939, aged 18. His family history and his previous history is of no consequence. He had always been shorter than other boys of his age, and his sexual development was that of a boy of about 8 years of age. Weight was 105 pounds. Height was 57 inches, span 60 inches, and the measurement from superior symphysis pubis to floor 29 inches, and from superior symphysis pubis to vertex 28 inches. There was no facial, axillary or supra-pubic hair. His voice was high pitched, his breasts were slightly enlarged. His penis was very small, the left testicle was in the scrotum but pea sized, and the right testicle could not be felt. Physical examination was otherwise negative (see photographs). Blood pressure was 110/76. His basal metabolic rate was −7%. The blood count was normal. Sugar tolerance curve: 1 hour, 70; 2 hours, 95; 3 hours, 90. Roentgen ray study revealed a delay in epiphyseal ossification. From October 31, 1939, to March 1, 1940, he received 1 cc. Anteron (400 U.) and 2 cc. Pituitary Alkaline Extract (Squibb), each three times weekly, without any change whatsoever. He was then placed on methyl testosterone 150 mg. per day, by mouth, for 5 months. The changes were striking—change in contour, configuration, genital growth, both testes are now palpable and larger, voice pitch lower, growth of supra-pubic and axillary hair, growth of 2 inches in height.

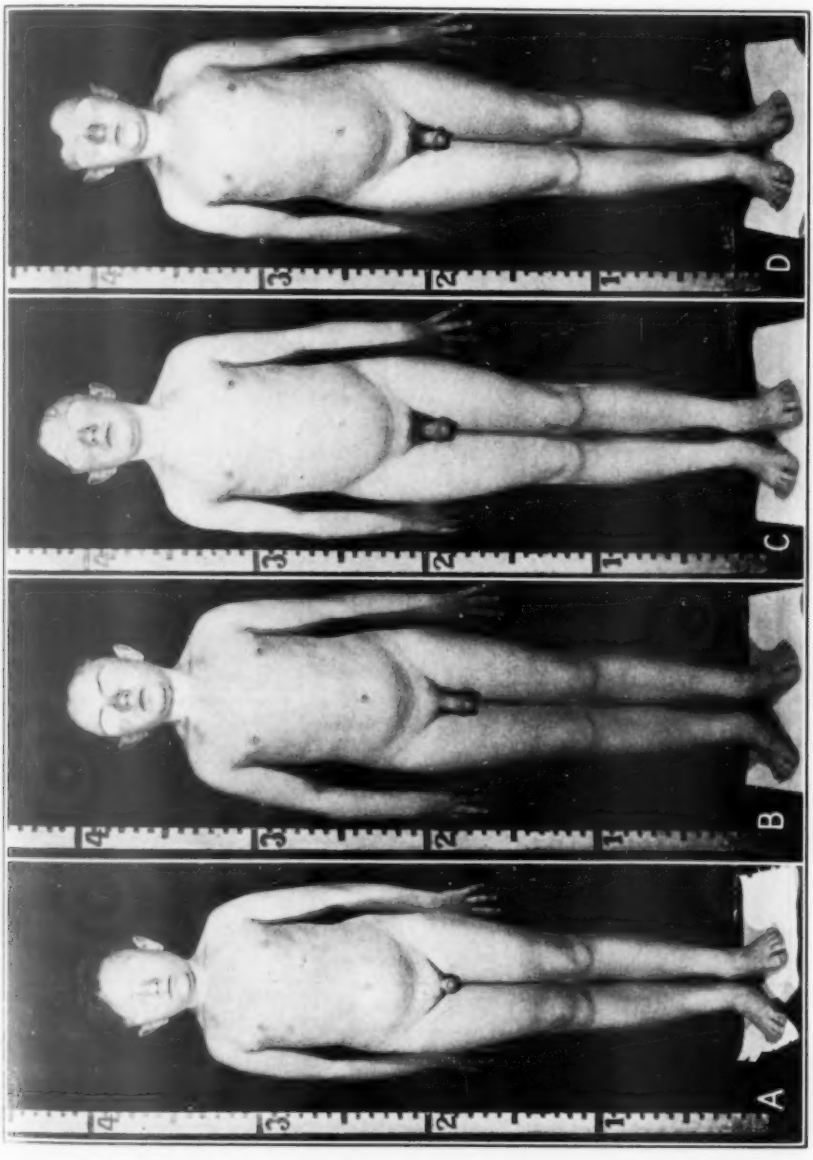
Case 4.—S. B., aged 16½, came to the clinic February 16, 1940. His family history was irrelevant. At 9 years of age an operation was performed for bilateral herniæ and undescended testes. There is no note as to

E. S.—12/21/39 E. S.—2/10/40



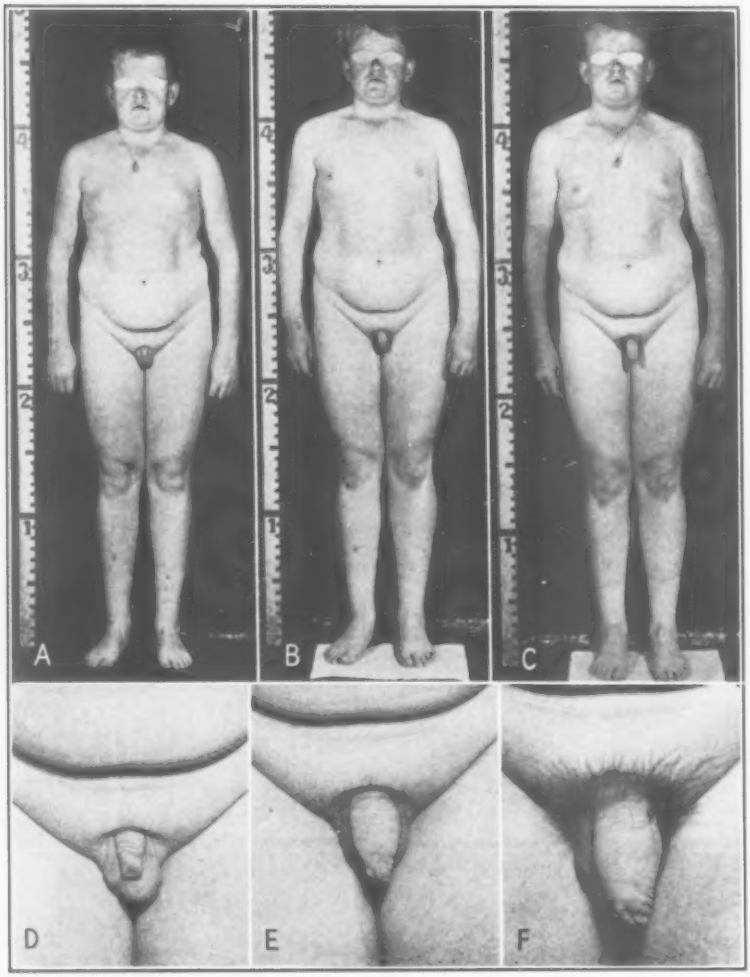
E. S.—12/21/39 E. S.—2/10/40

whether testes were found at operation. At 15 he had a course of 23 injections of A.P.L. (500 U. per cc.) with very little effect on genitals or hair growth. His complaints were the usual: lack of growth of penis, girdle obesity, enlarged breasts, high pitched voice, lack of supra-pubic, axillary and facial hair, complete absence of the normal sexual feeling. His weight was 135 pounds, his skin smooth, voice high pitched, breasts prominent,



and genitalia very small. No testes could be felt. Examination of heart and lungs were negative. Blood pressure 122/72. His height was 64 inches, span 68 inches, lower measurement (superior symphysis pubis to floor) $35\frac{1}{4}$ inches, upper (superior symphysis pubis to vertex) $28\frac{3}{4}$ inches. Roentgen ray

C. B.—10/15/39 C. B.—6/3/40 C. B.—8/6/40
March 1, 1940, also as above

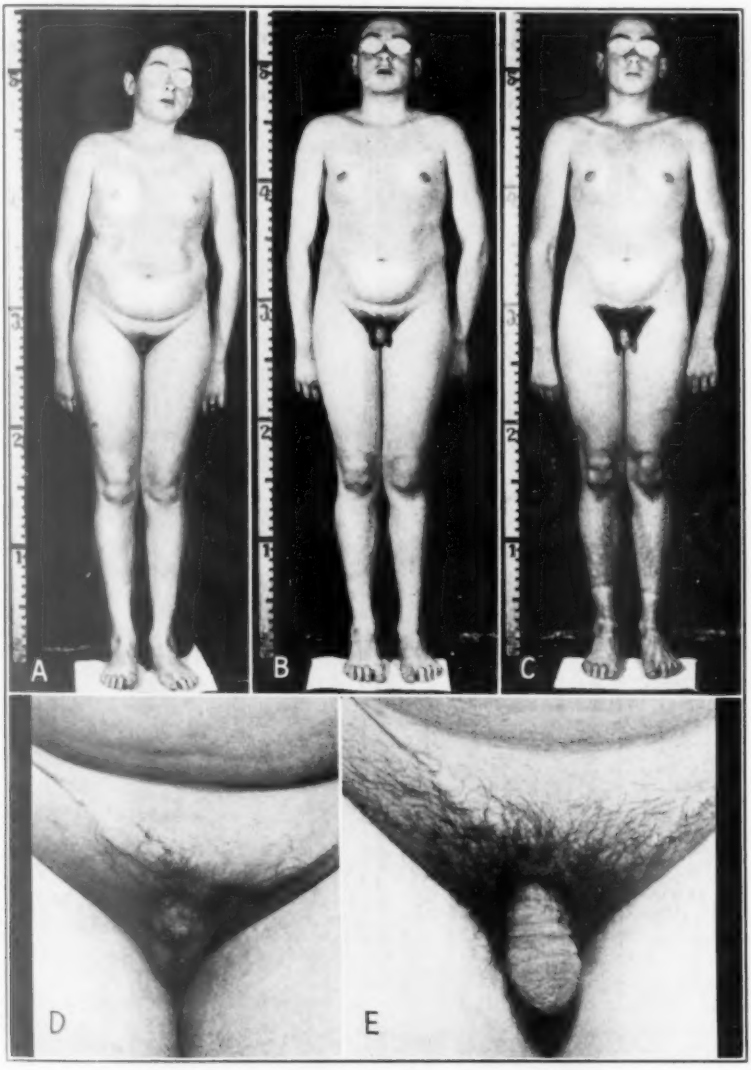


C. B.—10/15/39 C. B.—6/3/40 C. B.—8/6/40

examination of wrists showed normal epiphyseal development for his age. From February 23, 1940, to June 9, 1940, he received 150 mg. methyl testosterone per day, and from June 7, 1940, to September 7, 1940, 100 mg. per day. The changes have been marked and dramatic—growth in size of genitalia, growth in supra-pubic, axillary, and facial hair (he shaves twice

each week, which is an unusual observation or result), numerous and frequent erections, voice is now deep and masculine, increase in stature and change in body configuration.

S. B.—3/1/40 S. B.—5/18/40 S. B.—8/16/40



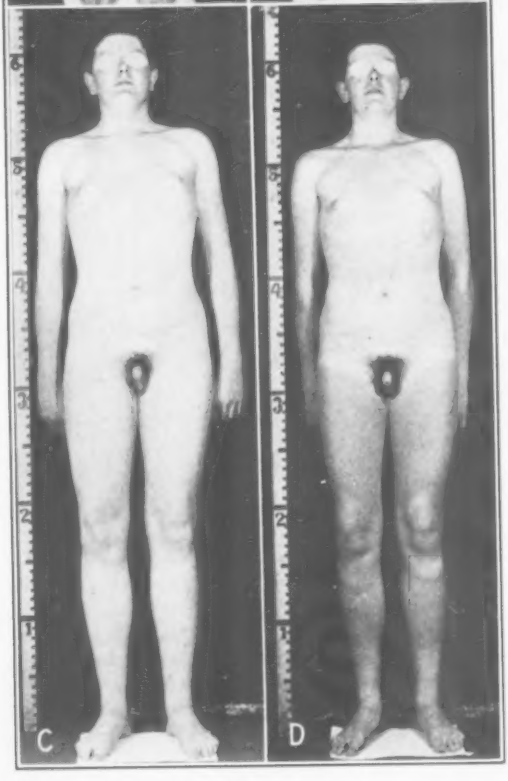
S. B.—3/1/40 S. B.—5/18/40

CASE 5.—T. McG., aged 22, admitted on December 1, 1939. His family and previous history apparently is without significance. He complained of an awareness of genital underdevelopment and inadequate secondary sex

T. McG.
1/2/40

T. McG.
2/8/40

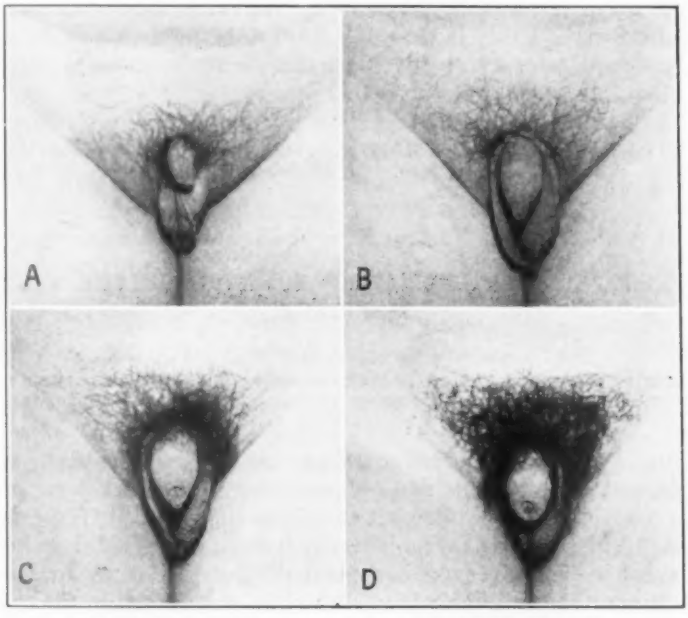
T. McG.
5/24/40



T. McG.
10/3/40

characteristics, since the age of 16, when contact with other boys brought this to his attention. There was a slight amount of libido, and an occasional erection. He was a tall, moderately obese boy with long lower extremities, Height was $71\frac{3}{4}$ inches, span 74 inches, lower measurement 40 inches, upper $31\frac{3}{4}$ inches. Weight was 180 pounds. Slight divergent strabismus. Heart and lungs were normal. Blood pressure 120/65. Slight gynecomastia. There was no facial, nor axillary hair, and a few supra-pubic. Penis was very small, and scrotum small and thin. Right testicle was not felt, while the left was "lima bean" in size. The Roentgen ray photographs of the sella turcica was normal, while the wrists showed delayed bone development, and the epiphyses were open. The basal metabolic rate was −13%. Sugar tolerance curve: 1 hour, 70; 2 hours, 90; 3 hours, 80. On January 6,

T. McG.—1/2/40 T. McG.—2/8/40



T. McG.—5/24/40 T. McG.—10/3/40

1940, treatment with methyl testosterone was commenced, 50 mg. three times daily, by mouth. Within 2 weeks, the penis was larger, reddened, and erections more frequent. The progression was steady, continued and marked—growth of penis and scrotum, left testicle larger, marked growth of supra-pubic and axillary hair, general configuration and appearance more mature and masculine. He gained 10 pounds in weight. There was marked libido and frequent erections. From February 1, 1940, to March 1, 1940, he had edema of the extremities, which was unexplained, excepting as possibly a testosterone effect.

Summary and Conclusion. Methyl testosterone, administered by mouth, 100 to 150 mg. per day, was beyond all doubt effective in inducing testosterone effects in several different types of patients, all

with hypogonadism. Its continued use maintained the effects of testosterone administration. In general, it appears that the earlier changes may be brought about more rapidly by injections of testosterone propionate. All the observations originally made following injections of testosterone propionate in such cases were found in this group with oral administration. Further observations, time, and individual case variations will determine dosage, duration of therapy, regression following discontinuance, and unusual or toxic responses. We feel that toxic or unusual responses are minimal, as are those of testosterone therapy in general. None of the patients complained of gastric distress or upsets. The time of dosage or its relation to meals apparently made little, or no difference. The extremes in variation of response may be due to individual case variations or require further study in dose. Methyl testosterone orally appears to be a good, safe, substitutive form of male sex hormone therapy.

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THE SCOPE OF ARTIFICIAL IMPREGNATION IN THE BARREN MARRIAGE.

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The involuntarily barren marriage continues, as it has for ages, to present an important medical, economic, and psychologic problem. The oft-quoted statement that from 10% to 15% of marriages in the United States are involuntarily barren, while coldly accurate, does not sufficiently express the appalling degree of marital insecurity and the deep unhappiness which lie submerged in the statistics. It is, therefore, the duty of any physician consulted by a barren couple to appreciate the complexity of the situation and to bend his every effort to the solution of the difficulty. From the standpoint of the required systematic survey, it is essential that *both* partners be assiduously investigated for possible etiologic factors and that any possible impediment, however slight, be removed. The methods of making an organized search in each marital partner and the means of treatment, having been clearly described in recent years,[7,8] are not within the province of the present essay.

This presentation is concerned with the relatively small group of childless couples who, having been thoroughly studied and, perhaps, treated, find themselves in the unhappy estate of unilateral barrenness—a dilemma in which the female is theoretically fertile

and the male alone is absolutely sterile. Is it the privilege of such unblest women, lucklessly mated to sterile husbands, to achieve maternity artificially? The moral and legal aspects of this question are, for the present, difficult to crystallize, but from the physiologic viewpoint the response is unequivocally affirmative. It must, nevertheless, be admitted that it is well-nigh impossible to apply the medical answer without due consideration to the two imponderable components of the question.

If an absolutely irremediable barrier to fertilization is found in the husband and if the wife, after complete study, is potentially fertile, it is then incumbent upon the physician to explain the hapless predicament to the barren couple. The physician should not attempt to sway the judgment of the couple but should merely discuss with them the need of adjusting their marital philosophy to that of a childless union; or, if they so please, the advisability of adopting one or more children. Occasionally, it will be suggested by one of the partners that the wife submit to artificial impregnation or, as the lay magazines state, "have a test-tube baby." The physician need assume no particular responsibility if one of the first two courses is chosen, but his burden is, indeed, heavy should the couple elect the last-mentioned procedure.

The occurrence of normal pregnancy following the artificial transfer of semen to the reproductive tract of the female is not a a newly discovered phenomenon. The fourteenth-century legend of the warring Arabian tribesmen who, in the dead of night, successfully inseminated the well-bred mares of their enemies with semen obtained from inferior stallions is often related as the origin of the procedure. The first successful experimental fecundations were those of Jacobi who, in 1700, was able to fertilize artificially the eggs of fish.[4] Nearly a century later, the Abbé Spallanzani succeeded in artificially impregnating a spaniel bitch.[11] The first successful artificial impregnation in a human female is credited by Home[6] to John Hunter who allegedly related the occurrence of such a pregnancy following the transfer to the vagina of semen from a husband with hypospadias. In the United States, Marion Sims was the first to employ this modality in sterility. In 1866, Sims[10] reported that 1 of 6 intrauterine inseminations had been successful. Since that time, as reviewed recently by Cary,[2] many gynecologists have recorded their experiences with artificial impregnation. The procedure is currently in the limelight because of the keener interest in barren marriages and because, as knowledge concerning the menstrual cycle and ovulation accumulates, such inseminations are more often successful. The recent questionnaire survey[9b] of 30,000 physicians, conducted by the National Research Foundation for Eugenic Alleviation of Sterility, shows that at least 9000 live children were produced by artificial impregnation in this country up to June, 1940.

Indications for Artificial Impregnation. The indications for artificial impregnation in instances of sterility, though limited and well defined, vary with the type of insemination to be employed. The procedure may be either *homologous*, when the husband's semen is artificially transferred to his wife's reproductive tract, or *heterologous*, when the semen of a stranger is employed.

Homologous insemination is indicated in the presence of either penile or vaginal malformations which prevent the normal deposition of semen in a couple otherwise potentially fertile. Thus, either hypospadias or pronounced vaginal atresia may constitute an indication for homologous insemination. A persistently acid reaction of the cervical mucus, as described by Guttmacher and Shettles,[5] may be considered an indication for homologous insemination of the intrauterine type. The procedure is, however, of no value in the management of ordinary sterility wherein one attempts, as Guttmacher[4] states, "to give the spermatozoa a 3-inch boost on their 6-inch journey."

Heterologous insemination, utilizing the semen of a donor, is indicated when it has been positively determined that the husband is absolutely sterile, as in either total aspermia or irreparable azoöspermia, and that the wife is potentially fertile. The latter statement implies definite knowledge that the Fallopian tubes of the wife are normally patent, that there is no cervical infection, and that the uterus is not underdeveloped. It is obviously important that the wife be free from any constitutional or local disorder which would make pregnancy hazardous. Heterologous insemination is the type usually employed, because absolute sterility of the male is more common than genital malformations of either partner. For this reason, certain prerequisites to its success, as well as the technique, are herein discussed.

Moral and Legal Aspects of Heterologous Insemination. The conditions imposed upon the physician who consents to perform artificial impregnation in a potentially fertile woman, with semen from a donor other than the husband, include the proper selection of couples in which such a procedure may be risked and the careful choice of a suitable donor.

In selecting the couples, it must be ascertained that both husband and wife are equally earnest in the request that artificial impregnation be performed and that both of them fully grasp the psychologic and emotional dangers which surround such a procedure. It is best to delay the proposed insemination for several months in order that the physician may assure himself that the husband's interest is not abnormally heightened by sheer bravado in an attempt to escape the self-accusations of inferiority. By thus familiarizing himself with the character of the husband, the physician is aided in his determination to avoid any future marital discord.

As a medicolegal safeguard, written permission for the impregnation should be obtained from both partners. The author does not deem it wise or necessary to establish all of the ceremonious legal formalities which Seymour and Koerner[9a] suggest. Several possible legal charges have been mentioned by both lay and medical writers as constituting serious obstacles, namely, a violation of the law by all concerned, the crime of adultery by the wife, and the aspersion of bastardy on the heir. There being no law, written or unwritten, concerning the legality of the act, the participation by anyone in the execution of artificial impregnation is not a statutory offense. The question of adultery is a debatable one, even though someone has said that "it is difficult to conceive of adultery being consummated in a test-tube." The common law, upon which most decisions concerning adultery would rest, considers adultery to be linked to the concept of sexual intercourse, an element lacking in artificial impregnation. However, as Beardsley[1] points out, the Supreme Court of Ontario, in 1921, sustained a charge of adultery by stating, "The essence of the offense of adultery consists not in the moral turpitude of the act of sexual intercourse, but in the voluntary surrender to another person of the reproductive powers or faculties of the guilty person." If such a decision were generally upheld, it could be made to affect all women who submit to artificial impregnation.

The legitimacy of the child born of artificial impregnation is a delicate question. As a general rule, most statutes protect any child born in wedlock from the aspersion of bastardy. However, even though the presumption of legitimacy is one of the strongest presumptions of the law, it is not absolute under all circumstances. It is easily controverted by proof of the husband's sterility. Therefore, in order to avoid any future shadow of bastardy and to guard the property rights of the child, whose inheritance privileges may be challenged by greedy relatives who by chance acquire knowledge of the manner of conception, it is best to establish protective measures at the time. The suggestion of Seymour and Koerner[9a] that, after pregnancy results from artificial impregnation, another physician—one ignorant of the origin of the conceptus—be engaged to complete the obstetric care does not solve the problem. The advice of the Legal Bureau of the American Medical Association[3] that the husband institute formal adoption proceedings as soon as the child is born, while certainly a safe course, seems to be unnecessarily public. Once a man has accepted a child born to his wife as his own, the law almost guarantees the legitimacy and, therefore, the inheritance of that child. Thus, in the author's opinion, the signed, witnessed consent of both marital partners for the performance of artificial impregnation, to which the husband has appended the affirmation that the child is his and his legal heir,[1] constitutes sufficient legal protection for all concerned.

The selection of a donor entails the impersonal purchase by the

physician of semen from a healthy, fertile male of good character and favorable heredity—one who has no evidence, clinical and serological, of ever having had either gonorrhea or syphilis. The donor must, moreover, be unknown to the barren couple. The request by the couple that a member of the family be employed as the donor should be categorically denied. It is obviously important for esthetic, moral, and psychologic reasons to preserve the anonymity of the donor. It is best that the donor selected be of the same racial strain as the husband and, if at all feasible, possess some of his physical characteristics.

Technique of Artificial Impregnation. The success of any insemination hinges on the potential fertility of the wife, as previously mentioned, on the excellence of the donor's semen, and on the timing of the insemination. The manner of introducing the semen into the vagina is the simplest part of the procedure. The donor is instructed to obtain the semen by manual masturbation, collecting it in a sterile, dry, glass vial and keeping it at room temperature until used. The semen should be introduced into the recipient as soon as possible after its collection, certainly within an hour. The specimen should be examined microscopically, as a check, when it is received from the donor.

The wife is advised to have intercourse with her husband, *if* he has no pyospermia, just prior to reporting for the insemination, with the hope that an imminent ovulation may be hastened and that favorable cervical secretions will be stimulated. If intercourse with her husband is not feasible, the woman is advised to take a preliminary vaginal douche with 2.5% solution of sodium bicarbonate. The temporary alkalinity of the vagina thus achieved may enhance the fertilizing ability of the spermatozoa. With the patient in the usual lithotomy position and the table tilted to the Trendelenburg angle, the specimen of semen is then merely squirted against the external os *without exposing the cervix*. For this purpose, it is convenient to use a sterile, dry, glass syringe and a blunt, 16-gauge needle. The patient is kept on the table in the Trendelenburg position for 30 minutes and is then permitted to follow her customary duties.

There is nothing to be gained, in the author's experience, by introducing the semen directly into the uterine cavity through a small rubber catheter or a Keyes-Ultzmann cannula. In fact, the results of the intrauterine method may be inferior because of the expulsive contractions of the uterus evoked by stimulation of the internal os. It is imperative, when the intrauterine technique is employed, to allow the uterine spasm caused by the passage of the catheter or cannula to subside before introducing no more than 0.5 cc. of the semen. A larger quantity of the semen tends to distend the uterine cavity and may give rise to undesirable contractions.

The timing of the artificial insemination so that it coincides with ovulation is obviously of paramount importance. When the wife is

able, because of either habitual midcycle pain or cyclic expulsion of clear cervical mucus, to foretell accurately the time of ovulation, the problem is simplified. If, however, no signs suggestive of ovulation are available, as is usually the case, 2 or 3 inseminations during the midportion of a single cycle should be performed. When failure occurs, even after such multiple inseminations, the days of the cycle selected should be altered at the next trial. In one of the successful cases herein reported, for instance, pregnancy did not occur after inseminations on the 11th and 14th days of the menstrual cycle but did follow subsequent inseminations on the 12th and 15th days. It is obvious that a large element of chance is involved in the meeting between a highly fertile ovum and a spermatozoön of similar quality. Seymour and Koerner[9b] recently reported that the average number of inseminations successfully employed by more than 4000 physicians was 12. This number of attempts was distributed in many ways, such as 1 insemination per month for 12 months, 2 inseminations per month for 6 months, and so forth. It is significant that 124 physicians reported successful artificial impregnation after as many as 21 inseminations. The patient, donor, and physician must be prepared, therefore, to repeat the procedure many times before meeting with success. The patient and donor will be more coöperative, if this is explained prior to the undertaking.

The recent observations of Guttmacher and Shettles[5] on the cyclic penetrability of the cervical mucus to spermatozoa may obviate the necessity of multiple inseminations. These authors recommend the application of a micro-technique for the repeated study of the penetrability of cervical mucus and record several successful inseminations during the so-called optimal phase of maximum spermatozoal penetration. The method described appears to deserve future study and trial.

TABLE 1.—DATA CONCERNING SIX ARTIFICIAL IMPREGNATIONS WHICH RESULTED IN NORMAL INFANTS AT TERM.

Patient.	Age.	Condition of husband's semen.	Number of inseminations.	
			Per menstrual cycle.	Total.
1	28	Azoöspermia	1	1
2	39	Azoöspermia	1	1
3*	31	Aspermia	2	10
4*	32	Aspermia	2	4
5	30	Azoöspermia	2	6
6	28	Azoöspermia	3	9

* The same patient; impregnations performed 18 months apart.

Report of Cases. The author has had the privilege of attempting heterologous artificial impregnation in 6 barren women whose husbands were absolutely sterile (Table 1). Five of the 6 women became pregnant and delivered healthy offspring. One of the 5 was successfully impregnated twice. The number of inseminations

received by these 5 women before pregnancy occurred varied from 1 to 10 (Table 1). The infants delivered, now ranging in age from 2 years to 6 months, are normal in every respect. The remaining patient is still undergoing repeated inseminations and, although 4 pairs of inseminations have been unsuccessful, one may not yet classify this as a failure.

Summary. 1. The legal and moral aspects of artificial impregnation, though not yet clearly defined, are discussed.

2. The history, indications, and technique of artificial impregnation are briefly stated. It is shown that the procedure may be easily accomplished if certain rules concerning the selection of the semen and of the potentially fertile wife are followed.

3. Six successful instances of artificial impregnation are herein recorded.

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OBSERVATIONS ON THE ORAL ADMINISTRATION OF RAGWEED OIL IN PATIENTS HYPERSENSITIVE TO RAGWEED OIL.

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It has been observed for some time that ether-soluble fractions of various plants were relatively common causes of contact dermatitis. The type of plants causing eruptions have been well recognized in the different geographical areas of this country. The specific management of patients manifesting plant oil dermatitis has not been adequately approached. For this reason further recorded observations in desensitization to plant oils seem justified.

Contact dermatitis treated by specific desensitization is regarded with great skepticism. This view would appear to be based upon

few observations. Jadassohn[4] described a case of desensitization in mercury idiosyncrasy, Riehl[7] in arsphenamine dermatitis; Urbach[10] in resorcin and in arsphenamine dermatitis, and Richter[6] in contact dermatitis of various origin. Blumenthal and Jaffe[1], in a sizable group of contact dermatitis cases, found desensitization unsuccessful except for the oil group. In one patient with multiple plant oil sensitivities these authors found a highly specific desensitization to an oil of lavender.

There is general agreement that contact dermatitis due to oils is the type that offers the best chance for specific desensitization. In this country, Caulfeild,[3] Seyler,[8] Shelmire,[9] and many others have published favorable results with specific desensitization to plant oils. On the other hand, Brunsting and Williams[2] express a negative view about the therapeutic value of desensitization, especially in ragweed oil dermatitis.

For the most part, plant oil[10] desensitization has been attempted by hypodermic injection or by external application. Dunkan and Dakins, however, are among the few who have tried oil by mouth. These authors recommended chewing the leaves of Rhus and swallowing the juices. Perutz[5] gave turpentine by mouth. According to American Indian folk lore, the early tribes had the habit of chewing the green leaves of plants belonging to the Rhus Toxicodendrum group as a means of preventing summer skin eruptions. The literature would infer that this procedure gave good protection to the tribesmen but often resulted in a temporary acute skin eruption and a temporary general debilitation.

Our observations were made in a group of 16 patients, all of whom manifested a typical contact dermatitis. In these cases we tried specific desensitization for the purpose of clearing the individual eruptions and to protect the patient against further attacks. For the most part we dealt with an isolated farmer population. Since under these circumstances regular treatment by hypodermic inoculation proved to be a difficult procedure, we gave the oil by mouth.

The essential details of occupation, patch test results, duration of the eruption, and season of the disease are detailed in Table 1. All of the cases manifested their eruption on the exposed surfaces; in Cases 2, 3 and 5, in addition to the exposed surface, the eruption occurred over both legs from the knees to the ankle, explainable on the basis of contact by walking in hay and fields containing the ragweed plant. Fifteen of the 16 patients had seasonal exacerbations of their eruptions occurring at the time of good development of the ragweed plant and during the season of ragweed pollination. Three of the patients had their eruptions throughout the year but they were always worse from mid-August through September, explainable on the basis of constant contact with hay which contained ragweed plants. All of the patients gave a 4+ positive patch test reaction to oil of ragweed in dilution of 1 to 1000 or higher dilution after

24-hours' exposure. Positive patch tests occurred to other chemical substances but the clinical picture and history in every instance would exclude other substances as being of practical clinical importance.

TABLE 1.—CLINICAL DATA IN 14 CASES OF RAGWEED OIL DERMATITIS.

Case no.	Name.	Age.	Onset.	Season.	Site.	Occupation.	Treatment ragweed oil.	Patch test.	Results.
1	J. L.	47	42	Chiefly Aug.-Sept.	Exposed surfaces	Farmer and mechanic	1 gtt. D. 1/200	4+ 1/1000	Complete relief 3 years
2	H. M.	60	57	Late Aug.	Exposed surfaces	Caretaker on farm	1 gtt. D. 1/500	4+ 1/200	Summer relief 1936–1937
3	H. J.	58	55	Start June, early Sept.	Exposed surfaces	Mechanic; gardner	Up to 5 gtt. D. 1/100	4+	Unsatisfactory
4	L. G.	45	36	Late Aug. to Nov.	Exposed surfaces	Truck driver	2 gtt. T.D.	4+	Unsatisfactory
5	J. A.	55	50	Mid-summer mid-winter	Shoetops to knees	Farmer	5 gtt. D. 1/100	4+	Fair
6	C. W.	51	47	Entire year worse in summer	Shoetops to knees	Farmer	1 gtt. D. 1/10,000	Alfalfa oil 4+	Fair
7	C. H.	73	60	Entire year worse in summer	Exposed surfaces	Farmer	1 gtt. D. 1/10,000	4+ 1/10,000	Complete relief 2 years
8	L. M.	29	27	July to Nov.	Exposed surfaces	Unemployed	1 gtt. D. 1/100,000	4+ 1/100,000	Complete relief 3 years
9	R. C.	54	48	Aug. to Nov.	Exposed surfaces	Farmer	1 gtt. D. 1/100,000	4+ 1/1,000,000	One season good
10	W. G.	41	37	Entire summer	Exposed surfaces	Lives in field	1 gtt. D. 1/400	4+ 1/1000	One season complete relief
11	J. H.	53	51	Aug. to Sept.	Exposed surfaces	Factory	1 gtt. D. 1/10,000	4+ 1/10,000	Four years satisfactory relief
12	J. M.	46	44	July to Nov.	Exposed surfaces	Farmer	1 gtt. D. 1/20,000	...	One season complete relief
13	A. T.	65	58	July to Aug., mild all year	Exposed surfaces	Farmer	1 gtt. D. 1/200	4+	One season complete relief
14	E. W.	56	53	July to Nov.	Exposed surfaces	Miner	1 gtt. D. 1/10,000	4+ 1/10,000	One season complete relief

Preparation of Materials. The ether soluble residue of the ragweed plant used for diagnostic and therapeutic purposes in this study was prepared in the following manner: Fresh, healthy giant and dwarf ragweed plants were collected in early September. The plant was allowed to dry and the stems and leaves were then ground to a fine powder, an excess of commercial ether was added and placed in a tightly stoppered bottle. This mixture was allowed to extract at room temperature for the next 48 hours. The ether was allowed to

evaporate. The residue was warmed and diluted in serial dilutions of ten, with warm olive oil.

Method of Treatment. All of the patients were patch-tested with oil of ragweed in olive oil in dilutions 1 to 100, 1000, 10,000, 100,000, 1,000,000. Treatment was begun with the drop of a dilution which gave a faintly positive 24-hour patch-test reaction. The oil was dropped on a teaspoonful of sugar by a non-ragweed oil sensitive person and taken by the patient each morning before breakfast. The chart further lists the doses of ragweed oil, the duration of treatment and the results obtained. Emphasis is placed upon the variability of the dosage. This has depended upon the degree of skin hypersensitiveness of the individual patient to ragweed oil.

Discussion. We wish to emphasize that the dosage of ragweed oil administration depends upon the patch-test reaction. It is recommended that all patients start with one drop of a strength solution which gives the faintest possible positive 24-hour patch-test reaction. In Cases 1, 2, and 3, administration of 1 drop of ragweed oil in 99 parts of olive oil on 2 successive mornings produced a generalized eruption characteristically similar to the eruption of external application of the oil. Repeating the same dosage following complete clearing of the eruption resulted in a second exacerbation in all 3 of the patients. They were, however, able to tolerate a dosage of 1 drop of 1 to 10,000 dilution which gave them complete protection from their usual daily exposure.

The fact that all of our patients gave a good positive patch-test reaction to oil of ragweed pollen makes it understandable why our patients have their eruption only during the pollen season or are worse during the period of pollination of the ragweed plant.

By repeated quantitative patch testing we have observed a reduction in the quantitative patch-test reaction in Cases 1 and 2. Before treatment, they reacted positively in dilutions 1 to 100,000, and after 2 years of continuous treatment they reacted only in dilutions of 1 to 1,000 in Case 1, and 1 to 200 in Case 2. In 5 others (Cases 3, 5, 6, 7, 10) there has not been a quantitative reduction in the patch test but in spite of this fact they are symptom-free.

Twelve of the 16 ragweed oil sensitive patients have been satisfactorily controlled with oral desensitization to ragweed oil. Two of the failures have not followed treatment sufficiently to justify an evaluation of therapy. We are unable satisfactorily to explain the failure in the other 2 patients.

Patients 3 and 4 were treated while they were in an exacerbation (September) with no appreciable benefit, suggesting that long continued treatment is necessary for a good therapeutic result.

Conclusions. 1. Sixteen patients with contact dermatitis due to hypersensitiveness to oil of ragweed were treated by oral administration of ragweed oil; 12 experienced satisfactory results.

2. It would appear that actual desensitization can be accom-

plished in plant oil contact dermatitis by oral administration of the specific oil.

3. Oral administration of oil of ragweed in greater than tolerance dose results in a generalized eruption of the contact type. Involvement, however, is maximum at the site of the previously involved areas.

4. Oral treatment with ragweed oil must be daily and continuous over long periods of time.

5. Oral desensitization to ragweed oil is recommended when there is a long intervening period before the expected time of contact with the plant or its pollen.

6. The therapeutic dose and overdose of ragweed oil are in close proximity. The estimated therapeutic dose, therefore, can best be determined by quantitative patch tests.

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CLINICAL INVESTIGATIONS WITH CURARE IN ORGANIC NEUROLOGIC DISORDERS.*

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Curare, known to South American Indians for generations, has been known to medical science for only about 100 years. Since time immemorial, the native Indians have used small amounts of gum curare upon arrow tips to paralyze game in hunting. Generalized muscular paralysis and respiratory death occur within a few minutes after injection of curare into the animal. The secrets of curare preparation have been carefully guarded and much "black magic" obscures its manufacture.

Now and then small amounts of the crude drug have been brought back to civilization since the time of Raleigh. In 1815, Watterton and Brodie demonstrated asphyxia to be the cause of death. Baussingault and Roulin in 1824, extracted the alkaloid curarin. In 1844, Schomburgh named the plant group *Strychnos toxifera*.

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In 1844, Claude Bernard first described the physiologic action of the drug upon the neuromuscular junction and confirmed asphyxia as the cause of death. Others contributing to our knowledge are Preyer, who, in 1864, isolated curarin in crystalline form; Pelouse and Lapique, who reported physiologic observations confirming the pure myoneural action of the drug.

Jousset, Demine and Busch in 1867, first attempted to apply the drug to clinical medical therapy. They treated convulsive states, epilepsy, rabies, chorea, strychnine poisoning, and various tics. Hoffman (1879), Hoch (1894), and Cash (1901), also experimented with curare. Tsocanakis, in 1924, tried curare in spastic paralysis. Bremer[3], in 1929, proved that the drug exhibited a selective action in reduction of local tetanus and decerebrate rigidity. West[7] (1931–35) and Cole (1934) reported partial results in the relief of tetanus convulsions, rigidity of Parkinsonism causalgia, and spastic paraplegia. Burman[4] (1938–39) reported extensively upon its relaxing effect in spastic, athetoid, and dystonic states of muscular rigidity and tremor.

A great drawback to experimental and clinical investigation of the drug has been the fact that no gourd or tube of crude curare made by one witch doctor would duplicate the ingredients of another, together with inaccurate information from native curare makers. Also, different curare plants from various areas give varying toxic action. Other lethal substances such as venom were added from time to time; these contaminants have snarled chemical and physiologic research. On the whole, pharmacologic literature gives the impression that the drug is highly toxic and dangerous, not applicable to clinical medicine. Furthermore, until recently, no large quantities of authenticated curare have been available at any one time for experimental research.

In 1934 Mr. Richard C. Gill[5], after exhaustive studies and prolonged contact with South American Indians, was able to learn the actual botanical ingredients and the secrets of manufacture. In 1938, he brought back to this country the largest amount of authentic and field-tested curare ever gathered and carried back to the civilized world. In addition, he returned with a large amount of unauthenticated curare, that is, curare from regions he had not personally visited. This supply was turned over to the E. R. Squibb and Sons' research department.

Standardization of the Drug. After considerable independent experimentation by Dr. A. R. McIntyre, Professor of Pharmacology at the University of Nebraska, and by Mr. H. A. Holaday, head of the biologic development and control division of Squibb and Sons'* biologic laboratories, the technique of standardization, at first difficult, has been simplified. Biologic methods of assay are neces-

* I am indebted to E. R. Squibb & Sons and Dr. Sidney Newcomer for furnishing standardized curare (Intocostrin) in these experiments.

sary with each new batch of the drug. The curare itself is extraordinarily stable, not destroyed by autoclaving. Assay by a variety of methods gives a result so precise that recheck reveals an error within the limit of 1%.

Methods of Assay. Curare-acetylcholine antagonism upon a frog gastrocnemius preparation has been applied in the study of methods of purification and in dilution control. A frog gastrocnemius preparation is made which, with addition of acetylcholine, produces an isometric type of contraction which furnishes a reference height for comparisons with a decreased height contraction obtained through the inhibiting effect of the curare solution. The method is applicable only when controlled by a reference standard qualitatively identical with the test material.

Another method of assay is the head-drop method in the rabbit, developed by Holaday. The curare solution is injected slowly into the ear vein of the rabbit and the dose adjusted so that the neck muscles after 2½ to 3 minutes reach a degree of flaccidity which just prevents the animal from raising the head and keeps the chin down. This end point is very clear cut and a typical curare effect occurs exactly as seen in the human after injection of a curarizing dose. The amount per kilogram necessary to produce this effect in the rabbit is estimated and the dosage is figured according to body weight of the patient.

Physiologic Action of Curare. Action of pure curare is upon the neuromuscular mechanism. In certain impure preparations, another action is seen, ascribed by Burman to curarin. This side-effect is a histamine-like action producing sudden fall in blood pressure, bronchial spasm, facial pallor, erythema, and urticaria, which is relieved by epinephrine. These preparations we have not employed clinically but are investigating them further. We believe them unsafe for clinical use.

The action of curare is upon the net-like structure of fine nerve fibers at the terminus, called the motor end plate. It is here that acetylcholine, the chemical mediator or regulator of chronaxie of nerve impulses to voluntary muscle, acts. Curare prevents acetylcholine from acting on the nerve muscle junction and inhibits its action, thus producing a paresis of muscle. Curare poisoning (curarization) thus prevents the transmission of natural nerve impulses from motor nerves to the muscles. This peripheral motor flaccid paralysis affects, in general, the nerve endings of all striated or voluntary musculature, but selectively affects, first, the fine fast moving muscles of high chronaxie, such as short muscles of the eyes and throat; later, the larger, slower moving muscles of head, neck, extremities, intercostals, and diaphragm.

The circulation is relatively unaffected and sensory nerves are not affected. While reflexes may be somewhat diminished they are not abolished. Death occurs from asphyxia due to respiratory paralysis.

The so-called lethal point of the drug is questionable because large doses are tolerated if respiration can be continued. The drug is quick acting and very rapidly eliminated. The rapidity of absorption has much to do with lethality. Small amounts of the drug injected rapidly are toxic and produce cardiac failure in animals while large amounts may be given slowly without toxic symptoms. Fifty times the lethal dose has been given to dogs by Dr. A. R. McIntyre without fatality by keeping up artificial respiration.

The physiologic effects are noted immediately at the end of an intravenous injection given over a period of 1 to 2 minutes. In about 2 more minutes the peak of curarization is reached, whereupon the effect slowly recedes and seems to vanish in 15 to 20 minutes. The same effect occurs in from 15 to 30 minutes after intramuscular injection. Physiologic symptoms are seen in the following sequences: The patient first complains of haziness or fuzziness of vision. Next, bilateral ptosis appears with slight nystagmoid movements, relaxation of the face and heaviness, with relaxation of the tongue and jaws. The patient at this point complains of tightness of the throat and huskiness of the voice. Generalized heaviness and weakness of the neck muscles with inability to raise the head are followed by weakness to complete paresis of the spinal muscles, legs and arms. Last, appears shallowness of respiration from weakness of the intercostals and the diaphragm.

These symptoms follow the same order as the progressive symptoms of a patient with myasthenia gravis; double ptosis and nasal smile also simulate those of the myasthenic. Excess saliva may accumulate in the throat and the patient complain of difficulty in breathing, but this occurrence is counteracted considerably if the relaxed jaws and tongue are held forward. Injections of epinephrine, prostigmin, or metrazol all seem to counteract quickly the action of curare. Burman believes that a sustained, clinically relaxing effect upon hyperkinetic or spastic muscles remains for a long period of time after the toxic deacetylcholinizing effect of curare has disappeared. We have not yet been convinced of any such prolonged action from curare. In fact, its usefulness is hindered by this temporary effect in spastic states. The only evidence we have for a possible prolonged action is the fact that a second intravenous injection in animals, if administered within 1 to 5 hours after an initial dose, will be more effective (depending upon the time interval), so that less curare is required to cause paralysis. In giving a second intravenous injection to patients after complete curarization seems to have disappeared, we have also noted it takes a lesser amount of curare to produce paralysis. The observation indicates that there is considerable prolongation of effect or retention of active alkaloid.

There are a number of drugs known to have a curare-like action: Quinine methochloride, erythroidine hydrochloride, ammonium

bases, amides and amines, choline, muscarin, snake venoms, methyl strychnine, aromatic series, pyridin, quinolin, thallin, nicotine series, piperidin, putrefactive ptomains, and products of muscular metabolism. References to the action of these drugs can be found in pharmacologic literature. One will be discussed later in this paper.

After extensive experience with curare, [1] developed a method of preliminary curarization of the patient prior to metrazol convulsive shock therapy which has completely removed all traumatic hazards of that treatment. The technique of this therapy has been described elsewhere.

Some clinical neurologic disorders resemble curare poisoning. Botulism, the food poisoning from improperly sterilized canned foods, produces a peripheral motor paralysis with respiratory failure resembling curarization. Acute ascending Landry's paralysis, often erroneously called acute poliomyelitis, is in reality an obscure toxic condition with an almost pure peripheral motor paralysis progressing until all voluntary musculature is involved, ending in respiratory paralysis and death from asphyxia. Myasthenia gravis, as noted earlier, in the progression of symptoms with its characteristic rapid fatigue of muscle from faulty function of the neuromuscular junction due to loss of acetylcholine, resembles mild curare poisoning. Both curare poisoning and myasthenia symptoms are immediately relieved by prostigmin.

Clinical Application of the Drug. The use of curare in clinical medicine must still be regarded as experimental. A large amount of investigative pharmacologic research and clinical experimentation must be carried out before curare can find a useful place in medical therapeutics. Yet, there is a tremendous potential usefulness for a safe drug with a curare-like action. The results from curare therapy up to the present have been inconclusive, owing to the fact that adequate supplies of standardized material have been almost impossible to obtain. This problem has now been overcome and the drug has proved to be indispensable in preventing complications of convulsive shock therapy.

In the field of neurology curare may find its greatest usefulness. West has reported interesting results with curare in the treatment of tetanus. In lockjaw, the violent muscular contractions become almost constant tetanic convulsions, finally exhausting the patient and ending in death. The recognized but not too effectual treatment is tetanus antitoxin. Greatly needed is a method of continuously relaxing the muscular spasms until the patient can develop an immunity against the toxin of tetanus bacilli. Curare, theoretically, offers such hope of preventing exhaustion, by relaxing the muscular spasms and producing a generalized peripheral muscular paresis.

The drug may also prove useful in controlling other convulsive states such as strychnine poisoning, eclampsia hydrophobia, and

status epilepticus. It should be possible to suppress these spasmodic disorders by sustained "physiologic" doses of curare. In well chosen cases a slow acting curare would be life saving as continued convulsions heighten fatigue. Even near-lethal doses might be administered with the aid of artificial respiration by means of a respirator. Certainly, experimentation with curare is worthy of trial in any convulsive disorder that is endangering life.

A most promising field for a curare-like drug is in the so-called spastic paralytic states. Infantile cerebral palsies, spastic paralysis, or Little's disease, usually the result of birth accidents, are responsible for one of the largest groups of cripples. No medical treatment has been previously known for these disorders. Orthopedic treatment, surgery, and physiotherapy for muscle training have been all that could be offered. Curare releases the spasm and muscle rigidity and involuntary tremor and spasms disappear through relaxation. While these effects are not curative, the transient relaxing effect enables the paralytic patient to talk better, use the hands for finer movements such as feeding, writing, and so on, and permits relaxation of the limbs. Such added benefit enables the orthopedic surgeon to use braces more effectively and to carry out necessary surgery of fixed deformities. The problem is to get a drug with a prolonged action. At present curare action is too fleeting; a slow sustained effect is essential. After obtaining the drug effect, there is still the problem of muscle reëducation through physiotherapy exercise to learn new control of formerly helpless muscles. The child is able to gain faster as a result of the relaxing effect of curare. Much investigative research is necessary before this treatment can be successfully applied.

There are a number of other organic neurologic diseases characterized by rigidity of muscles and involuntary spasms and tremors from involvement of lower motor centers of the brain in the basal ganglia or striate system. Some of these are paralysis agitans, athetoid disorders, dystonia musculorum deformans, lenticular degeneration, multiple sclerosis, postencephalitic Parkisonism and oculogyric crises, Huntington's chorea, spasmodic torticollis, and hemiballismus. These are all disabling conditions and notoriously resistant to treatment. Small doses of curare cause a diminution in the hypertonia, tremor, and involuntary motility of these disorders, thus giving the patient marked temporary relief. Even though its use is not curative, it would enable the patient to live a life of comparative comfort. Here again, a slow-acting, sustained effect is necessary if the drug is to become a useful therapeutic aid.

Personal Experiences. 1. *Spastic paralysis.* A group of 12 severe cases of spastic paralysis were given curare injections every other day, 10 mg. per 20 pounds of body weight, for a period of 3 to 8 months. Each child was accepted for treatment from a large number of spastic cases because of some unusual or different symptom.

Eight of these children were under constant supervision at the Nebraska Orthopedic Hospital. Orthopedic procedures and physiotherapy were carried out at the same time. The following cases are examples of the results obtained:

Case Reports. Case 1.—E. B., aged 9, was the first child subjected to treatment because of the severity of the condition—a marked spastic tetraplegia with severe contractures of all extremities; incoördination and dysarthria were present. An attempt to release the contractures by casts had resulted in severe pressure ulcers and violent exhausting spasmodic contractions. All surgical attempts were unsuccessful; sedative drugs were likewise ineffectual. Curare therapy carried out over an 8-month period produced a marked improvement, enabling the patient to tolerate plaster casts and extension procedures to overcome fixed deformities.

Case 2.—R. M., aged 12, with severe spastic tetraplegia and marked athetosis and dysarthria, was unable to stand or feed herself. Curare treatment was directed toward improving the athetosis. This child was on treatment for 5 months. Slow but constant progress resulted in the child's becoming able to walk and feed herself. More rapid gain from physiotherapy was seen as a result of curare.

Case 3.—E. P., aged 18, had a severe spastic tetraplegia with marked involvement of the upper extremities, pronation contractures, athetosis, and dysarthria. Curare treatment was directed toward improving function of the arms and speech function. A 4-month treatment was carried out, but only transient, temporary improvement was noted in speech function and lessening of the athetosis.

Case 4.—A. P., aged 8, had severe spastic tetraplegia with contractures of all extremities, athetosis, dysarthria; he was unable to sit alone. Curare treatment directed toward relaxing spastic contractures and incoördination of the arms was carried out for 3 months. While a transient, temporary relaxing effect was noted no permanent gain occurred.

Case 5.—B. F., aged 7, had spastic tetraplegia with marked incoördination, dysarthria, and spastic contractures. Curare treatment, directed toward improving coördination and relaxing spasticity, was given over a 3-month period. The result was a slow, but sustained improvement, hardly attributable to curare since its effect was too transient.

Case 6.—B. L., aged 16, had spastic tetraplegia with dysarthria, spasmodic torticollis, athetosis, and spastic contractures. Curare treatment, directed toward spasmodic torticollis and athetosis, was given over a 4-month period. The result was temporary improvement after each injection, but again the curare effect was too transient and fleeting.

Case 7.—R. L., aged 12, had spastic tetraplegia with dysarthria, facial grimacing, mental retardation, and inability to hold up the head. Curare treatment directed toward the speech defect and grimacing was given over a period of 1 month, but was discontinued because of the hopeless prognosis.

1. *Comment on the Entire Group.* Curare produces a definitely but transient, relaxing effect upon spasticity without fixed deformity. It reduces incoördination, athetosis, and dysarthria. Favorable progress occurred in the majority of the patients while under curare therapy. The treatment is not dangerous and there are no toxic reactions.

A sustained curarization would be a valuable aid in the treatment of spastic paralysis and extra pyramidal rigidity states.

Five adult patients with spastic paraplegia caused by such diseases

as transverse myelitis and advanced multiple sclerosis have been given curare treatment. The drug will temporarily relax these spastic contractures but its effect is transient. It does, however, give patients relief from painful spasm and for this purpose alone can be recommended.

2. *Status Epilepticus.* We have had opportunity to study the effect of curare upon one case of status epilepticus. In a child with an obscure infection there developed toxic encephalitic symptoms with hyperthermia, a syndrome of decerebrate rigidity, spasmodic myoclonus with grand mal seizures that occurred every few minutes. These seizures were uncontrolled by various sedative drugs and ether anesthesia over a 10-day period. At the time curare was given, the child was moribund. Continuous intravenous curare injection was kept up for 12 hours. During this period the patient was completely relaxed and free of seizures and rigidity. The child died, apparently of cardiac failure, but necropsy examination was refused.

3. *Parkinsonian Syndrome and Paralysis Agitans.* Six patients with both encephalitic Parkinsonism, oculogyric crises, and paralysis agitans have been given curarizing doses of curare. The rigidity relaxes, tremor and oculogyric crises disappear, but as the effects of the drug wear off in about 1 hour, the former rigidity and tremor return. During this period the patient is unable to carry out active movements and complains of weakness. We see no advantage from the relaxation under curare over that obtained from belladonna-derivative antispasmodic drugs which can be given by mouth.

4. *Huntington's Chorea.* I have never observed any relief of involuntary movements of hereditary chorea from previous drug therapy. To 1 patient in private practice and 3 patients in a state hospital, I have given repeated physiologic curare injections. The incoördinate movements cease while curarization is present and slowly return to their former state within a few hours. These patients express gratitude for the relaxation obtained and ask for repeated injections. Again the drawback is the fleeting action of the drug which requires repeated injections. We are now experimenting with a synthetic drug with a curare-like action.

5. *Athetosis and Dystonia.* Besides the spastic paralysis combined with athetosis we have had the opportunity of studying the effect of curare upon adult athetotic, dystonic patients and upon post-encephalitic dystonic states. They relax temporarily for about 1 hour, after a curare injection. A patient had suffered from progressive, painful flexor spasms with athetosis and contracture of the right hand and foot for over 10 years. The etiologic factor was head trauma. Encephalographic Roentgen ray studies revealed atrophy of the basal ganglia, particularly on the left. All types of antispasmodic drugs and sedation had been ineffectual in relaxing the spasm or relieving athetosis. After a physiologic injection of curare, all evidence of contractural spasm and athetosis would dis-

appear and for several hours the patient would be free from pain. The effect, however, was fleeting and finally a premotor cortical resection was performed with permanent relief of the disorder.

6. *Hemiballismus.* (Syndrome of Corpus Luys.) We have recently had the opportunity of observing the effect of curare upon severe hemiballistic movements. A diabetic patient with evidence of generalized arteriosclerosis gradually developed severe chorea-like rolling, incoördinate movements of the left arm. These gradually spread, involving the left leg, trunk and face. After about 2 weeks of almost constant motion, the patient was admitted for hospital observation. The movements were not relieved by large doses of stramonium; under barbiturates the patient was able to obtain a few hours of sleep. After intravenous injection of aqueous curare, 10 mg. per 20 pounds of weight, complete relief from the movements was obtained for several hours. After intramuscular injection of concentrated curare, 20 mg. per cubic centimeters, the patient would fall asleep and obtain a full night's sleep. While these observations were being made, a pulmonary embolus suddenly developed and the patient died. Necropsy showed a thrombotic softening of the right globus pallidus and a small lesion of the right corpus Luys.

7. *Tetanus.* We have had opportunity to observe curare action in but 2 cases of tetanus. Both were moribund patients before curare therapy was attempted. In each instance, however, we have been able to produce relaxation of the continuous tetanic convulsion as long as curarization was continued. We believe it possible to perfect a continuous curarization technique that will prove to be extremely valuable in controlling convulsions of this disease. We believe that curare therapy offers more possibilities than sedative therapy in controlling tetanic convulsions.

Synthetic Curare. The collection and preparation of curare is a difficult task requiring expeditions by an expert explorer into South American jungles to procure adequate amounts of the potent nontoxic drug. We have, therefore, endeavored to find a drug with a curare-like action that would safely replace crude curare. Drugs having a curare-like action have been mentioned.

Quinine has been known for sometime to have a curariform action as shown by its relaxing effect upon myotonia congenita and dystonia musculorum deformans. It also aggravates the symptoms of myasthenia gravis. The commercially available quinine salts have a very weak curare-like action.

King[6] has shown that in curare there are certain tertiary ammonium bases. It has been known that quaternary ammonium compounds formed by the addition of alkyl radical to the nitrogen atom of the quinoline ring have a curare-like action. King prepared a synthetic compound called quinine methochloride formed by the addition of the methyl group to the quinuclidine nucleus of

the quinine molecule. Harvey[5] has shown that this drug has a strong curare-like action when administered either orally or parenterally.

Through the courtesy of E. R. Squibb and Sons research department, we were furnished with quinine methochloride for experimentation. An aqueous solution was prepared containing 20 mg. per cubic centimeter. Dr. A. R. McIntyre has compared in animals the reaction of quinine methochloride given intravenously with that of curare. He found with the former a curare-like action but not a pure curare effect as reported by Harvey. In the dog, the effect of quinine compared with that of curare is a rather marked drop in blood pressure with diminished respiration before complete cessation of nerve muscle contraction occurs; whereas the pure curare effect shows complete curarization of muscle or blocking of nerve impulses without any demonstrable drop in blood pressure or marked change in respiration. However, a definite transient paresis of muscles is produced, very similar to the action of curare, and in the patient is indistinguishable from curarization.

We have reported elsewhere[2] that the flaccid paresis following intravenous injection of quinine methochloride, 8 to 10 mg. per kilo, is sufficient to protect the patient from fractures in metrazol convulsions. In spastic paralysis we are able to obtain a complete curariform action after intravenous injection of 10 to 15 mg. per kilo of body weight. This curare effect wears off in from 10 to 15 minutes or can be completely counteracted by an intravenous injection of 1 to 2 cc. of prostigmin. A curarization effect can be produced by oral administration with about 8 times the intravenous dosage.

In 8 cases of spastic athetoid paralytic states and 1 case of Huntington's chorea, marked relaxation of rigidity and abolition of involuntary movements resulted from oral administration of 3 to 4 gm. (45 to 60 gr.) of quinine methochloride daily. The patients experienced marked subjective relief and definite objective improvement occurred while the patients were taking the drug. While these observations are based upon a very few cases, we believe that they are sufficient to conclude that this drug has possibilities for useful application to hyperkinetic and spastic neurologic disorders.

Summary. 1. Curare has successfully been applied to clinical neurologic therapy.

2. Its use as a preventive of traumatic complications in metrazol convulsive shock therapy has been proved.

3. Experiments with curare suggest an etiologic factor in botulism, ascending Landry's paralysis, and myasthenia gravis.

4. In spastic paralysis, athetoid and dystonic states, Parkinsonism, hereditary chorea, spasmodic torticollis, status epilepticus, tetanus and hemiballismus, curare produces a marked relaxation of rigidity and abolition of involuntary movements. Its action is

transient and fleeting, but continued experimentation should evolve a sustained action that will be therapeutically valuable.

5. A synthetic drug, quinine methochloride, has a curare-like action that is effective by mouth. This drug offers great possibilities, not only as a replacement drug for metrazol convulsive shock therapy, but in clinical neurology to relax hyperkinetic, spasmodic, and spastic states.

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BOOK REVIEWS AND NOTICES

RADIOLOGIC PHYSICS. By CHARLES WEYL, S. REID WARREN, JR., and DALLET B. O'NEILL, the Moore School X-Ray Laboratory, Moore School of Electrical Engineering, University of Pennsylvania. With a Foreword by EUGENE P. PENDERGRASS, M.D., Director of the Department of Radiology, University of Pennsylvania. Pp. 459; 166 illustrations. Springfield, Ill.: Charles C Thomas, 1941. Price, $5.50.

THIS book is the result of extensive teaching experience obtained from courses given to graduate students and Roentgen ray technicians since 1930. As a result, the exposition is clear and comprehensive. From the fundamentals of elementary electric and magnetic phenomena the reader is carried smoothly into analyses of electric circuits and electronics. Next electromedical apparatus is briefly covered with an excellent outline of high-voltage generators for Roentgen ray equipment. Part 2 of the book begins with the theory of radiation, including both the wave and the quantum theories, and goes into the production of Roentgen rays and their interaction with matter. The chapter on radioactivity and nuclear physics is a considerable aid in understanding the contemporary theories and applications of natural and artificial radioactivity. The remaining quarter of the body of the book is devoted to measurement, control and use of Roentgen rays and gamma rays in therapy, roentgenography and fluoroscopy. The appendix covers the elements of algebra, trigonometry and calculus, together with a four place table of logarithms, a table of exponentials and a table of natural trigonometric functions.

The subject material is well handled and there are many cross-references and excellent illustrations. There is an adequate bibliography at the end of each chapter. The book should be a great help to the student and Roentgen ray technician, and a good source book for the radiologist.

G. H.

AGE MORPHOLOGY OF PRIMARY TUBERCLES. By HENRY C. SWEANY, M.D., Medical Director of Research, Municipal Tuberculosis Sanitarium, Chicago, and Research Associate, Department of Physiology, University of Chicago. Pp. 265; 73 plates and 26 charts. Springfield, Ill.: Charles C Thomas, 1941. Price, $5.00.

THIS book is of primary interest for pathologists but is of clinical importance as well. The author has attempted to set up criteria through which the age of primary tubercles can be determined by pathologic examination. He has reached these criteria by tracing the microscopic changes in a large series of primary tubercles of approximately known age, the latter being determined on the basis of known exposure to open tuberculosis in early life. The changes as represented by development and regression of successive anatomic phases in the tubercle have been weighted in a chart that the author has devised for determining the age of primary tubercles of unknown history.

Two chapters are of special concern for clinical medicine, *viz.*, one on the age of tubercles found in a group of nurses and hospital attendants, the other on the age criteria of primary tubercles as revealed by roentgenography. In this day when much attention is devoted to the question of transmission of tuberculous infection in hospitals, and to the respective rôles of exogenous and endogenous infection, the author's effort to date

the oldest tuberculous lesions in the body is timely. Unfortunately much less can be learned by roentgenography in life than by pathologic examination at necropsy. Only 20% of primary lesions are visible in antemortem films, and after calcification has become complete, a process consuming ordinarily 6 to 8 years, further changes that are conspicuous in microscopic sections cannot be detected by roentgenography.

The author's method of approach is logical and the conclusions impress the reader as sound. The book is well organized and the illustrations are numerous and excellent. The press work is commendable in every way.

E. L.

MacLeod's Physiology in Modern Medicine. Edited by Philip Bard, Professor of Physiology, Johns Hopkins University School of Medicine, with 9 Collaborators. Pp. 1256; 387 illustrations. Ninth edition. St. Louis: The C. V. Mosby Company, 1941. Price, $10.00.

Three years ago in its English edition, this standard textbook of physiology was completely revised, each section having been assigned to a specialist. This highly successful arrangement has been continued in the present edition. Revision is again extensive, the sections on circulation, respiration, metabolism and nutrition having been entirely rewritten, and a chapter added on the bladder. The quality of paper has been improved. In general, the new edition is a considerable improvement in a book already excellent.

M. McC.

Green's Manual of Pathology. Revised and Enlarged by H. W. C. Vines, M.A., M.D., Director of the Charing Cross Hospital Institute of Pathology. Pp. 1166; 701 illustrations. Sixteenth Edition. Baltimore: The Williams & Wilkins Company, 1940. Price, $8.50.

By greatly enlarging the book, revising some sections and rewriting others, a practically new textbook of pathology has been produced. The conventional division into the two sections of general and special pathology has been preserved. The inclusion of the avitaminoses in the chapter in general pathology on diseases of nutrition seems to the Reviewer most appropriate.

Despite a certain unevenness, the book as a whole is well suited to the needs of the beginner in pathology. Its value in stimulating the student to enlarge his knowledge by outside reading is greatly diminished by the omission of all references to the literature. It is to be hoped that the next edition will include a bibliography and that certain errors in the present one will be corrected, such as "Evehejm" for "Elvehjem" (p. 108), "vitamine" for "vitamin" (pp. 102–110) etc., and that a reference to the literature will make it clear whether "Meakin" or "Menkin" is meant (p. 133) in connection with fibrin formation and the localization of inflammation. The illustrations are very numerous, but some could be omitted without great loss.

E. W.

The Therapy of the Neuroses and Psychoses. A Socio-Psycho-Biologic Analysis and Resynthesis. By Samuel Henry Kraines, M.D., Associate in Psychiatry, University of Illinois, College of Medicine; Assistant State Alienist, State of Illinois, etc. Pp. 512; 3 figures. Philadelphia: Lea & Febiger, 1941. Price, $5.50.

This book, written by a psychiatrist for those not specializing in psychiatry, goes a long way in practical guidance. Most of the space is devoted to the analysis of neurotic symptoms and to the treatment of

neurotic patients. Neurotic symptoms are divided into those expressing tension and those used as symbols, a very helpful and clear way of presenting what are widely considered as meaningless phenomena. The reality of these symptoms is made more evident by the excellent passage showing the rôle of the autonomic nervous system in the production of tension symptoms. This discussion leads naturally into a simple, well documented, and specific treatment of psychosomatic isorders.

The suggestions given for therapy, while not of a very profound nature, are quite sound and practicable. There is an abundance of illustrative case material presented. The author has the happy faculty of presenting the best in psychobiology in a clear and simple way that will do much to take the mystery out of psychiatric practice.

The small amount of space given to the psychoses seems justified for the reason that by and large those not practising psychiatry will not have psychotic patients under their care. Manic-depressive psychoses are categorically called "physiologic illnesses." Convulsive therapy is highly recommended for the treatment of depressed patients, especially those in the involutional period. In regard to the insulin therapy of schizophrenia, the highly controversial statement is made that "the principle of this form of treatment is to produce some 15 to 25 insulin comas in the patient. This number is generally sufficient to cure most patients."

There are several other opinions about which the reader should be warned because they are stated as facts. "Cures are not more commonly obtained by psychoanalysis than by eclectic psychiatrists, and what cures are achieved through the psychoanalytic technique of treatment occur because its therapeutic value lies not in its elaborate superstructure . . . ." "These same goals (of psychoanalysis) can be achieved far more simply and directly by the therapy as advanced elsewhere in this book . . . ."

The author seems to feel that analysts would recommend psychoanalysis as superior form of therapy for all neuroses. This is, of course, not true and casts some doubt on the author's opinion in regard to Psychoanalysis in general.

Despite the above criticisms and an overly optimistic view prevailing throughout, this book is highly recommended to those for whom it is intended.

L. S.

AN INTRODUCTION TO DERMATOLOGY. By RICHARD L. SUTTON, M.D., Sc.D., LL.D., F.R.S. (EDIN.), Emeritus Professor of Dermatology, University of Kansas School of Medicine, and RICHARD L. SUTTON, JR., A.M., M.D., L.R.C.P. (EDIN.), Assistant Professor of Dermatology, University of Kansas School of Medicine. Pp. 904; 723 illustrations. Fourth Edition. St. Louis: The C. V. Mosby Company, 1941. Price, $9.00.

THIS work continues to be one of the best short texts in dermatology available to the student and general medical man. The need for 4 editions in 9 years is, in itself, a tribute to its excellence and popularity. The present revision is considerably improved by the inclusion of a short and carefully compiled bibliography of leading articles in the readily available journals and by the addition of numerous carefully selected illustration.

Although the section on syphilis covers many of the general medical and treatment aspects of the disease, it should not be regarded as adequate for the present-day needs of the student or general practitioner unless supplemented by considerable collateral reading.

The management of the common skin diseases is adequately covered and the majority of the rarer dermatoses are classified and briefly described.

N. I. JR.

RADIOLOGY PHYSICS. An introductory Course for Medical or Premedical Students and for all Radiologists. By JOHN KELLOCK ROBERTSON, F.R.S.C., Professor of Physics, Queen's University, Kingston, Canada. Pp. 270; 188 illustrations. New York: D. Van Nostrand Company, Inc., 1941. Price, $3.50.

THE author assumes as prerequisite for the use of his book a knowledge of many of the elementary aspects of mechanics, radiation, and electricity and magnetism. He uses it as a text for a course given during the last year of a 2-year course in physics for pre-medical students. Although his treatment of the subject of electricity is elementary, it is not fundamental, and therefore cannot initially help a reader who wants to review the fundamental bases of electricity and magnetism.

The material which is presented is in general accurate and clear and the sections on the Conductivity of Air, Chemical Analysis by Positive Rays, The Meaning of Critical Absorption Wave-length, Causes of Grid Shadows, Absolute Intensity and Law of Inverse Squares and particularly the sections on the Cyclotron and on Radioactivity are extremely well written and well illustrated.

This book will be useful to medical students, radiologists and possibly some radiologic technicians as well. E. P.

HUTCHISON'S FOOD AND THE PRINCIPLES OF DIETETICS. Revised by V. H. MOTTRAM, M. A. (CANT.), Professor of Physiology at King's College of Household and Social Science, University of London, and GEORGE GRAHAM, M. D. (CANT.), F.R.C.P. (LOND.), Physician to St. Bartholomew's Hospital. Pp. 648; 27 illustrations. Ninth Edition. Baltimore: The Williams & Wilkins Company, 1940. Price, $6.75.

A BOOK which has gone through 8 editions needs little comment. For those who are not familiar with it, a short outline may not be amiss. After some general observations on dietetics, the authors describe the functions of the foods in the normal diet, in providing energy and body building, with special chapters on the inorganic elements and the vitamins. The classes of foods are then taken up in greater detail with their composition and their place in the total dietary explained. Several chapters are devoted to the principles of feeding in infancy and childhood, and to the diet in the treatment of disease. These are so clearly presented that the fact that the details are based on English menus, tastes and meal hours, detracts only slightly from its value. Simple food tables make it easy to adjust the diet to any desired amount and distribution of the various foods.

The text is clear and readable and the index is sufficiently detailed so that no difficulty is found in locating any desired item. This book deserves the careful consideration of anyone desiring a book on dietetics. R. R.

ANUS, RECTUM, SIGMOID COLON. Diagnosis and Treatment. By HARRY ELLICOTT BACON, B.S., M.D., F.A.C.S., F.A.P.S., Clinical Professor of Proctology, Temple University School of Medicine; Associate Professor of Proctology, Graduate School of Medicine, University of Pennsylvania, etc. Introduction by W. WAYNE BABCOCK, A.M., M.D., LL.D., F.A.C.S., Professor of Surgery, Temple University School of Medicine. Foreword by J. P. LOCKHART-MUMMERY, M.A., M.B., B.C. (CANTAB.), F.R.C.S. (ENG.), Emeritus Surgeon, St. Mark's Hospital, London, England. Pp. 857; 507 text illustrations (mostly original) by WILLIAM BROWN MCNETT; 1 colored frontispiece. Second Edition. Philadelphia: J. B. Lippincott Company, 1941. Price, $8.50.

THE second edition of this work is very similar to the first. It is an excellent and painstaking review of the literature and description of the

various diseases of the anus, rectum and sigmoid colon. The author has kept the book abreast of the times by adding the newer methods and drugs as they are applied to diseases of the lower bowel. The illustrations by McNett are outstanding and probably account for much of the popularity of this work. This book remains as a very excellent reference work for surgeons and practitioners interested in a monograph concerning diseases of the lower bowel. L. F.

MODERN DRUG ENCYCLOPEDIA AND THERAPEUTIC GUIDE Presenting descriptions of 11,114 modern, non-pharmacopeal, ethical medicinal preparations in 15,629 forms, comprising: 3,421 drugs and chemicals, 663 biologicals, 691 endocrines, 2,270 ampoule medicaments, 3,190 individual and group allergens and 879 miscellaneous products. For the Use of Physicians, Dentists, Pharmacists, and Medical Students. By JACOB GUTMAN, M.D., PHAR.D., F.A.C.P., Director, Brooklyn Diagnostic Institute; Consulting Physician, Manhattan General Hospital, New York, the Riverdale, Shore Road, Williamsburg Maternity, and Borough Park General Hospitals of Brooklyn. Pp. 1644. Second Edition. New York: New Modern Drugs, 1941. Price, $7.00.

As outlined in the Preface to the first edition of this book in 1934, its purpose is to provide a concise yet adequate and authoritative source of information for the physician about the many products of pharmaceutical manufacturers that do not find their way into New and Non-official Remedies. The Encyclopedia part (1303 pages, with distributors' index) contains an alphabetical list of such preparations, giving for each the name of the manufacturer, the composition, the claimed action and uses, the form, or forms, in which it is supplied, and the recommended dosage; the listings are offered without comment or change from the original sources. Preparations advertised and sold directly to the laity are not included. The Therapeutic Index (339 pages, with drug index) is an alphabetical catalogue of disease states under each of which are listed the preparations in the Encyclopedia that are recommended in that connection. As a reference book this provides in compact form a source of information about the composition of preparations which are more or less widely used and it will therefore be valuable to pharmacologists and toxicologists. The scientific therapist will also be enabled by it to arrive at his own decisions as to the probable value of the remedies listed herein compared with the simpler and much cheaper official preparations. The Therapeutic Guide seems to the Reviewer to be a complete anachronism; the book would be more dignified and no less valuable without it. C. S.

ELECTROCARDIOGRAPHY IN PRACTICE. By ASHTON GRAYBIEL, M.D., Instructor in Medicine, Courses for Graduates, Harvard Medical School; Research Associate Fatigue Laboratory, Harvard University; Assistant in Medicine, Massachusetts General Hospital, and PAUL D. WHITE, M.D., Lecturer in Medicine, Harvard Medical School; Physician, Massachusetts General Hospital, in charge of the Cardiac Clinics and Laboratory. Pp. 319; 272 figures. Philadelphia, W. B. Saunders Company, 1941. Price, $6.00.

IN this atlas are illustrated the important abnormalities encountered in clinical electrocardiography. Brief case histories are supplied for correlation. Explanations are concise and clear. Of particular interest are the sections on the arrhythmias, and the considerable numbers of tracings showing borderline electrocardiographic abnormalities and their interpre-

tation. The inclusion of 129 "unknown" tracings toward the end of the book, with case histories and interpretations opposite, allows one to test his skill with that of the authors'. The Reviewer regrets that only one chest lead (*CF*–4) is used in the study of patients suspected of having coronary artery disease. W. J.

Biological Aspects of Infectious Disease. By F. M. Burnet, M.D., Assistant Director, Walter and Eliza Hall Institute, Melbourne. Pp. 310; 9 figures and 4 plates. Cambridge: The University Press; New York: The Macmillan Company, 1940. Price, $3.75.

Books on infectious diseases have usually been written by medical men who have been interested chiefly in the effects of infection on man. This book is written by a biologist to whom both man and microörganisms are objects of equal interest. It treats infections as interactions between living species, *i. e.*, infectious agents (protozoa, bacteria and viruses) and their hosts. The author emphasizes that "we can deal with no restricted field in studying the nature of disease. The whole range of living beings comes into our province, for there is probably no species of organisms which has not at one time been either host to a parasite, or a parasite itself. Infectious disease is universal." The host-parasite relation is discussed from the ecologic point of view, as a struggle for existence between species which profoundly affect one another. Broadly viewed, the interactions lead to its development of an approximately balanced condition.

There are chapters on the processes within the body of the host which develop as the result of invasion by infectious agents, on the natural history of infectious disease, of its spread, on the general character of endemic disease and of epidemics, on some important infections which exemplify general principles, and finally on new diseases and the outlook for the future.

The book is very readable and should serve as a stimulating complement to more orthodox textbooks. The general reader interested in the relation of biology to human affairs will find here an excellent account of infectious disease as an important aspect of everyday life. B. L.

The Comparative Physiology of Respiratory Mechanisms. (The William J. Cooper Foundation Lectures, 1939, Swarthmore College.) By August Krogh. Pp. 172; 84 illustrations. Philadelphia: University of Pennsylvania Press, 1941. Price, $3.00.

This book represents a series of lectures given at Swarthmore College. It should be a valuable addition to the literature on comparative physiology, and serve a useful purpose not only for students but also for teachers and research workers.

The respiratory mechanisms of numerous species from small invertebrates to whales and man are discussed. The various examples are arranged "into a kind of physiological system, built up on analogy of function." A large number of zoölogic forms are considered and the species are carefully indexed. In addition 287 references to the original literature are given, so that the book will provide a rich mine of information on respiratory function to the zoölogist and comparative physiologist.

Many of the chapters present relatively simple facts which should be understandable even to a beginner in the subject, but this does not imply that the same chapters are not invaluable to the expert. The charm of the book lies in the originality, simplicity and clarity with which relatively simple facts are arranged and analyzed. The master hand of one of the outstanding living biologists is throughout in evidence. H. B.

MASOCHISM IN MODERN MAN. By THEODOR REIK. Translated by MARGARET H. BEIGEL and GETRUD M. KURTH. Pp. 439. New York: Farrar & Rinehart, Inc., 1941. Price, $4.00.

MASOCHISM is the desiring of discomfort and pain, and Freud has regarded it as our most common and important perversion. After having pondered the subject for 15 years, the author believes he has solved many of its intricacies. Debt is acknowledged to Freud for his insight into the nature of masochism but it is said he failed to arrive at its full understanding—pointed the way but did not go. Reik's thesis is discussed in eight parts: Problem, Phenomena, Dynamics, Origin, Sexes, Ego-Gains, Social Forms and Cultural Aspects. It is maintained that sexual masochism embraces the paradoxical pairing of discomfort and pain with sexual pleasure. In social masochism, the martyr attitude of modern man is seen to have developed. Fear of annihilation of the personality and the hope of immortality has led to the national masochism of today. The author's theories are difficult to follow. Philosopher Havelock Ellis wrote most lucidly on masochism; failure to consider these discussions, particularly his case of "Florrie," is more harmful to the author than to the philosopher.

N. Y.

DEBATABLE TUMOURS IN HUMAN AND ANIMAL PATHOLOGY. (Cancer Research Memoirs, No. 1.) By W. F. HARVEY, E. K. DAWSON, and J. R. M. INNES. From the Research Laboratory of the Royal College of Physicians, Edinburgh, the Cancer Control Organisation of Edinburgh and South-East Scotland, and the Institute of Animal Pathology, University of Cambridge. Pp. 124; 40 plates. Edinburgh: Oliver and Boyd, Ltd., 1940, for the Cancer Control Organisation of Edinburgh and South-East Scotland. Price, 10/6.

BY "debatable tumours" the authors apparently do not mean lesions that are doubtfully neoplastic (though this idea also appears on occasions), but rather neoplasms the nature of which is debatable—as if this were not true to some degree for all neoplasms. The authors have selected for consideration 9 tumors which are "so debatable that a detailed argument on their nature seems justifiable." The seminoma they regard as a malignant epithelial tumor arising from the spermatoblast; the granulosa cell tumor as of primitive ovarian follicle origin; the "mixed tumor" of the parotid as an adenoma; the giant cell tumor of bone as a neoplastic growth intermediate between purely reactive tissue and a true blastoma. Among melanomas the authors include benign nevus cell tumors, and pigmented tumors of mesodermal origin; the malignant melanoma they regard as a melanocarcinoma. Endothelioma may be either benign or malignant, "vasoformative" or "membraneoformative"; meningioma arises from stem-cells of endothelial type. Lymphosarcoma arises from a primitive mesenchymal cell, which has "productive potentialities of endothelioblast, fibroblast and lymphoblast." The terms "reticulum-cell, lympho- and endothelial sarcoma" are used interchangeably. "Lymph epithelioma" is considered as covering two types of malignant growth: carcinoma and lymphosarcoma. The suffix "-blastoma" apparently is used to indicate malignancy.

Thus the reader may not infrequently find his tumor concepts at variance with the authors' views, who incidentally express regret for a dogmatism necessitated by limitations of space. He cannot fail to profit, however, from the clearly stated results of the obviously careful study of a large amount of tumor material. The numerous excellent photomicrographs and the bibliography of Directional Literature are also to be commended. The lack of an index is a striking defect.

E. K.

A TEXTBOOK OF CLINICAL NEUROLOGY. By J. M. NIELSEN, B.S., M.D., F.A.C.P., Associate Clinical Professor of Medicine (Neurology), University of Southern California; Senior Attending Physician (Neurology), Los Angeles County General Hospital; Attending Neurologist, Hospital of the Good Samaritan, Los Angeles. Pp. 672; 179 illustrations. New York: Paul B. Hoeber, Inc., 1941. Price, $6.50.

THIS is a very practical book written in plain language. Students and physicians alike will here find the answers to their neurologic problems. The clinical picture of the various diseases is built up on the anatomy of the diseased parts of the nervous system, their function and pathology. Photographs and diagrams facilitate the comprehension. The methods of differential diagnosis and treatment are clearly stated and the use of recent drugs such as the sulfonamides and the vitamins are discussed. The book is written, as the author explains, in a somewhat dogmatic style since the enormous material had to be limited in some way. It is unavoidable under these conditions that the author's opinion will not be always shared by others. This danger is lessened by bibliographies accompanying each chapter, giving the reader an opportunity to follow up details if he is interested in controversial questions. The presentation reflects throughout the experience of the author as neurologist and as teacher. The book is recommended as a textbook for students and as a reference book for physicians.

F. L.

SPERMATOZOA AND STERILITY. A Clinical Manual. By ABNER I. WEISMAN, M.D., Adjunct Gynecologist, Jewish Memorial Hospital; Clinical Assistant Visiting Gynecologist and Obstetrician, Metropolitan Hospital, New York. With a Foreword by ROBERT L. DICKINSON, M.D. Pp. 314; 77 illustrations. New York: Paul B. Hoeber, Inc., 1941. Price, $5.50.

THE present volume would be a useful addition to the library of the general practitioner, urologist and gynecologist. As its name implies, it is essentially a hand book of practice. Its contents deal primarily with the practical details of studying the seminal fluid, and the proper interpretation of the findings. An interesting part of the work concerns the question of artificial insemination and its medico-legal aspects. Other chapters deal with the author's original contribution to the subject. The material is well arranged, and the illustrations are excellent. The volume contains much that is of general interest, apart from its practical aspects. An excellent bibliography of some 764 titles is appended.

D. M.

ROENTGEN INTERPRETATION. By GEORGE W. HOLMES, M.D., Roentgenologist to the Massachusetts General Hospital and Clinical Professor of Roentgenology, Harvard Medical School, and HOWARD E. RUGGLES, M.D., Late Roentgenologist to the University of California Hospital and Clinical Professor of Roentgenology, University of California Medical School. Pp. 364; 246 illustrations. Sixth Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1941. Price, $5.00.

IN 1919, in the preface to the First Edition, the authors remarked that it was their hope that "this book will prove of particular aid to those in search of a working knowledge in roentgen interpretation." The fact that the work is now in its Sixth Edition bears ample testimony to the success of their purpose.

The outstanding characteristics of this work continues to be its clearness and brevity. As in the past, the authors have not attempted to present their material in an exhaustive fashion. Because of this, the manual is admirably suited for use by students and physicians other than radiologists.

The general characteristics of the book are unchanged, the illustrations are essentially the same. The authors have added to the chapter on Diseases of Bone, a brief résumé of sarcoidosis, Ollier's disease and the bone changes seen in erythroblastic anemia. A discussion on the recent advances in the diagnosis of intramedullary spinal cord tumors is also new. The chapter on Diseases of the Chest now includes references to mediastinal herniation, pericardial tumors, and tuberculous ulcerations of the bronchi associated with atelectasis. The diagnosis of lymphoblastoma of the lung are also included in this chapter. The chapter on the small intestines has been augmented by a discussion of small intestinal tumors.

Whereas the volume is well illustrated, it is hoped that the next edition will appear with positive illustrations changed to negative illustrations.

P. H.

THE MASK OF SANITY. An Attempt to Reinterpret the So-called Psychopathic Personality. By HERVEY CLECKLEY, B.S., B.A. (OXON.), M.D., Professor of Neuropsychiatry, University of Georgia School of Medicine, Augusta. Pp. 298. St. Louis: The C. V. Mosby Company, 1941. Price, $3.00.

THE individual commonly known as a "psychopath" is regarded by the author as psychotic and irresponsible, thus rendering him immune to punishment. But such subjects know the nature and quality of their acts of misbehavior, also that they are punishable; and knowing their weaknesses, it becomes their duty to fortify themselves by self-restraint; failing to do so, they render themselves liable to punishment. We already have a group whom psychiatrists regard as showing partial or limited responsibility, a condition which some courts recognize. While not offering a classification of his own, Cleckley comments favorably upon those of Noyes (who regards the condition as an expression of unconscious conflict) and of Kahn, who has made valuable contributions. There are 12 case reports revealing the disorder, and 6 others wherein it is partly manifested. Without clearly defining the condition, considerable space is devoted to its distinction from other personality disorders, some being the orthodox psychotic, the psychoneurotic, the mental defective, the ordinary criminal, sexual deviates, the erratic man of genius, the neurotic drinker, the malingerer, and fictional characters showing personality anomalies. While not solving this intricate problem, the author has given us an interesting treatise, including much pertinent matter by others. Being a writer of fiction also, he has employed a style less rigid than that of the scientist.

N. Y.

MANUAL OF CLINICAL CHEMISTRY. By MIRIAM REINER, M.Sc., Assistant Chemist to The Mount Sinai Hospital, New York. Introduction by HARRY SOBOTKA, PH.D., Chemist to The Mount Sinai Hospital, New York. Pp. 296; 18 illustrations and 17 tables. New York: Interscience Publishers, Inc., 1941. Price, $3.00.

THIS is a valuable little book of handy size. It is thoroughly practical, having had its origin in the need of laboratory interns for a source of precise technical detail "in the middle of the night." It is surprisingly complete and should appeal as a source of reference particularly to those lone and many-sided laboratory technicians in smaller hospitals who are not called on every day to do determinations which are routine matters in larger institutions. The contents are chiefly quantitative methods of blood and urine analysis, but there are also included the usual qualitative chemical

tests on urine, feces, spinal fluid and gastric juice. Unexpected welcome inclusions are some toxicologic tests, methods for sex hormones, Quick's prothrombin method, and technique of extracting allergens for subsequent skin-testing from naturally occurring source materials; also some photoelectric colorimeter methods, methods for vitamins, technique for biliary and urinary calculus analysis, and even the Takata-Ara test. For each method there is a key reference to the literature (all of which add up to a sizeable bibliography), and there is an author index. D. B.

MECHANISMS OF BIOLOGICAL OXIDATIONS. By DAVID E. GREEN, Senior Beit Memorial Research Fellow, Institute of Biochemistry, University of Cambridge. (Cambridge Biological Studies, General Editor, C. H. WADDINGTON.) Pp. 181; 22 figures. Cambridge: The University Press, 1940; New York: The Macmillan Company, 1941. Price, $2.75.

CELLULAR oxidation is one of the basic phenomena of life. This book treats of the mechanisms of biological oxidations and discusses the enzyme systems in the cells upon which oxidation depends. Although most of our knowledge of such mechanisms is derived from experiments on but a few types of cells, a great store of information is now available. This monograph gives an excellent summary of biologic oxidation by a well-known investigator who has made significant contributions in this important field. B. L.

A DIABETIC MANUAL FOR THE MUTUAL USE OF DOCTOR AND PATIENT. By ELLIOTT P. JOSLIN, M.D., Sc.D., Clinical Professor of Medicine Emeritus, Harvard Medical School; Medical Director George F. Baker Clinic at the New England Deaconess Hospital; Consulting Physician, Boston City Hospital. Pp. 238; 53 illustrations. Seventh Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1941. Price, $2.00.

THE seventh edition of this very useful book maintains the standard set by its predecessors. In addition to the information which the book contains, it continues to be written with that hope for the future of the well trained diabetic which the author knows so well how to present. Two chapters of questions and answers combine with easily understood diet instructions to make this a book without which no diabetic can afford to be. The physician also will find much here to interest him, especially as regards the newer advances in diabetes. R. R.

SCIENCE AND SEIZURES. New Light on Epilepsy and Migraine. By WILLIAM G. LENNOX, M.D., Sc.D., Hon. Assistant Professor of Neurology, Harvard University Medical School; Visiting Neurologist, Boston City Hospital; etc. Pp. 258; 10 figures. New York: Harper & Brothers, 1941. Price, $2.00.

CONSIDERATION of the nature and treatment of convulsive and headache seizures is the purpose of this book. In 1929, Hans Berger, German psychiatrist, demonstrated that when the electric currents of the brain were enormously amplified, they could be detected in the scalp and recorded on moving paper. The pattern of the resulting electroencephalogram (shortened to "E.E.G.") is quite characteristic of each individual. During a convulsion, the waves are increased in size and frequency. Grand mal shows a rapid dysrhythmia, in a psychomotor attack it is slow, and in petit mal the rhythm is alternating. A minor dysrhythmia is also present

when attacks are absent. Severe seizures may be predicted in advance. Sedation used in epilepsy, causes a slowing of cortical rhythms. Tantrums and some mental disorders show definite dysrhythmias. At present the matter of expense is a serious one; the instrument is expensive and a skilled operator and interpreter is required. In treatment, the new drug, dilantin sodium, is frequently of value. One notes that Napoleon has been omitted from the long list of great epileptics; Byron and Peter the Great should have been also. In migraine, it is the vegetative nervous system that is chiefly affected; there are no known brain changes. Ergotamine tartrate is a new and useful remedy, though considerable nausea follows its injection. Lennox has illuminated one of the dark realms of medicine. N. Y.

MANUAL OF PHYSICAL DIAGNOSIS with Special Consideration of the Heart and Lungs. By MAURICE LEWISON, M.D., Professor of Physical Diagnosis, University of Illinois College of Medicine; Consulting Physician, Cook County Hospital, etc., and ELLIS B. FREILICH, M.D., Associate Professor of Medicine, University of Illinois College of Medicine; Professor of Medicine, Cook County Graduate School of Medicine, etc. In collaboration with GEORGE C. COE, M.D., Instructor of Medicine, University of Illinois College of Medicine; Associate Physician, Cook County Hospital; Clinical Assistant, Mount Sinai Hospital, Chicago. Pp. 317; 75 illustrations. Chicago: The Year Book Publishers, Inc., 1941. Price, $3.00.

THIS manual is the outgrowth of the outline which the Senior author has used in teaching the principles of physical diagnosis to his students.

"Systemic examination" of everything above the clavicles is covered in 9 pages. Five pages are allotted to the physical examination of the upper and lower extremities and the joints. Neurological examination is confined to a description of reflexes in less than 3 pages. That portion of the book which deals with physical examination of the thorax and the abdomen is adequate.

The Reviewer suggests that, if this book reaches a second edition, sufficient space should be allotted to "systemic examination," examination of the extremities and joints and that a chapter be added on physical examination of the nervous system. The requisite space can be achieved by omitting Diseases of the Bronchi, Lungs and Pleura (23 pages) and Diseases of the Cardiovascular System including Chronic Valvular Heart Disease, Subacute Bacterial Endocarditis, Diseases of the Pericardium, Angina Pectoris and Coronary Occlusion, Aneurysm of the Thoracic Aorta and Congenital Heart Disease (15 pages). S. L.

MEDICINE AND HUMAN WELFARE (The Terry Lectures). By HENRY E. SIGERIST, M.D., D.Litt., William H. Welch Professor of History of Medicine in the Johns Hopkins University. Pp. 148; 20 illustrations. New Haven: Yale University Press, 1941. Price, $2.50.

THIS, the 16th volume of the Terry Lectures on "Religion in the Light of Science and Philosophy," conforms well with the aims of the Terry Foundation to advance the human race by promoting the interpretation of scientific discoveries and their application to human welfare. These lectures bear on religion, broadly interpreted, in the same sense as do earlier ones in the series, such as Compton's "Freedom of Man," and Bareroft's "The Brain and Its Environment."

The present series explores one of Dr. Sigerist's leading beliefs—the need for a better application of the triumphs of medical science to a basically changed society that is still in a period of transition. The first section, on

disease, shows the changing attitude toward disease through the centuries and touches on historic pestilences as examples of social illnesses that profoundly affected society. The second section, on health, considers the ups and downs of hygiene in ancient, medieval and modern times. Among the topics considered are: the Greek and Roman successes in attaining a sound mind in a sound body, Johann Peter Frank and the concept of governmental control of public health in the 18th century, Chadwick and the English public health movement in the 19th, the failure of the German national health program of a century ago, and the gradual growth, with the development of medicine and engineering sciences, of a public health movement reaching well beyond the fields of sanitation and communicable diseases. In the third section, a survey of the physician's activities through the ages leads up to his widened sphere in today's social structure, including his integral relations to the law, education, industry and so on. Recognizing that the "technology of medicine has outrun its sociology," Dr. Sigerist proposes the drastic remedy that the physician be removed from the competitive business of private practice and that ultimately medical care be made a free public service. Though he recognizes that the financing of health care by taxation or insurance must depend to some degree on circumstances, he obviously favors the Soviet system of health planning, training of personnel and the prevention and treatment of disease as entirely a function of the government.

In their judicious selection from a great wealth of material and their dignified, entertaining style, these lectures present in attractive form an aspect of modern medicine that is of the highest importance for all physicians to comprehend and consider, even if they may not agree with the conclusions drawn and inferred. E. K.

PEDIATRIC BIBLIOGRAPHY. By A. GRAEME MITCHELL, Department of Pediatrics of the College of Medicine, University of Cincinnati, and The Children's Hospital Research Foundation, Cincinnati. (Monographs of the Society for Research in Child Development, Vol. VI, No. 1, Serial No. 27.) Pp. 119 (lithoprinted). Washington, D. C.: Society for Research in Child Development, National Research Council, 1941. Price, 75c.

A WORKING bibliography of Pediatric literature based on material gathered mostly by Dr. J. P. C. Griffith and his colleague, Dr. A. G. Mitchell for their textbook. It makes no pretense of being complete for the field of Pediatrics or for any one subject but will be useful as a springboard to any specific section or disease of childhood. E. T., JR.

NEW BOOKS.

Oral Pathology. A Histological, Roentgenological, and Clinical Study of the Diseases of the Teeth, Jaws, and Mouth. By KURT H. THOMA, D.M.D., Professor of Oral Surgery, and CHARLES A. BRACKETT, Professor of Oral Pathology, Harvard University. Pp. 1306; 1370 illustrations, including 137 in color. St. Louis: The C. V. Mosby Company, 1941. Price, $15.00.

Das Vitamin K und Seine Klinische Bedeutung. By DR. FRITZ KOLLER, Privatdozent für Innere Medizin an der Universität, Zürich. Mit Einem Geleitwort von PROF. DR. W. LÖFFLER, Zürich. Pp. 151; 15 illustrations. Leipzig: Georg Thieme, 1941.

Medical Manual of Chemical Warfare. (First American Edition; Reprinted by Permission of The Controller of His Britannic Majesty's Stationery Office.) Pp. 119; 1 figure and 10 plates. Brooklyn: Chemical Publishing Company, Inc., 1941. Price, $2.50.

The Medical Clinics of North America, Vol. 25, No. 3 (New York Number, May, 1941). Pp. 265; 8 illustrations. Philadelphia: W. B. Saunders Company, 1941.

Hernia. In Three Sections. Historical Evolution of Hernial Surgery; Technical; Medico-legal Aspects. By ALFRED H. IASON, B.A., M.D., Consulting Surgeon, Long Beach Hospital; Director of Surgery, Brooklyn Hospital for the Aged; Surgeon, Manhattan General and Madison-Park Hospitals, etc. Pp. 1325; 355 illustrations by ALFRED FEINBERG, Instructor of Medical Illustrations, Department of Pathology, College of Physicians and Surgeons, New York City. Philadelphia: The Blakiston Company, 1941. Price, $15.00.

Biology of the Laboratory Mouse. By The Staff of The Roscoe B. Jackson Memorial Laboratory. CLARENCE C. LITTLE, Director, GEORGE D. SNELL, Editor, J. J. BITTNER, A. M. CLOUDMAN, E. FEKETE, W. E. HESTON, W. L. RUSSELL, G. W. WOOLLEY. With a Chapter on Infectious Diseases of Mice by J. H. Dingle, Harvard Medical School. Pp. 497; 172 illustrations. Philadelphia: The Blakiston Company, 1941. Price, $7.00.

The British Encyclopedia of Medical Practice Including Medicine, Surgery, Obstetrics, Gynæcology, and Other Special Subjects. *Complete Index.* Under the General Editorship of SIR HUMPHRY ROLLESTON, BT., G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge; Sometime President of the Royal College of Physicians of London. With the assistance in a consultative capacity of F. R. FRASER, M.D., F.R.C.P., Professor of Medicine, University of London, etc., G. GREY TURNER, D.Ch., M.S., F.R.C.S., F.R.A.C.S., F.A.C.S., Professor of Surgery, University of London, etc., JAMES YOUNG, D.S.O., M.D., F.R.C.S. Ed., F.C.O.G., Professor of Obstetrics and Gynæcology, University of London, etc., SIR LEONARD ROGERS, K.C.S.I., M.D., LL.D., F.R.C.P., F.R.C.S., F.R.S., Late Physician, Hospital for Tropical Diseases, London, and F. M. R. WALSHE, O.B.E., M.D., Sc.D., F.R.C.P., Physician in Charge of the Neurological Department, University College Hospital. Pp. 486. London: Butterworth & Co. (Publishers), Ltd., 1941. Price, $10.00.

Conditioned Reflexes and Psychiatry. (Volumes 1 and 2 of Lectures on Conditioned Reflexes. Twenty-five Years of Objective Study of the Higher Nervous Activity [Behavior] of Animals.) By IVAN PETROVITCH PAVLOV, Late Director, Physiological Laboratories, Institute of Experimental Medicine and Academy of Sciences, Leningrad; Late Professor of Physiology, Military Medical Academy, Leningrad, etc. Translated and Edited by W. HORSLEY GANTT, M.D., B.Sc., Medical Director, Leningrad Unit American Relief Administration, 1922–23; Co-worker in Pavlov's Laboratory, Institute of Experimental Medicine, 1925–29; Associate in Psychiatry and Director, Pavlovian Laboratory, Johns Hopkins University. (Vol. 1 with the Collaboration of G. VOLBORTH, M.D., Former Assistant to Professor Pavlov at the Military Medical Academy; Professor of Physiology, University of Kharkov, and an Introduction by WALTER B. CANNON, M.D., S.D., George Higginson Professor of Physiology, Harvard University.) Pp.: Vol. 1, 414 and 9 illustrations; Vol. 2, 199 and 7 illustrations. New York: International Publishers, 1931. Price, Vol. 1, $3.50; Vol. 2, $4.00.

Essentials of Endocrinology. By ARTHUR GROLLMAN, PH.D., M.D., Associate Professor of Pharmacology and Experimental Therapeutics in the Medical School of The Johns Hopkins University. Pp. 480; 74 illustrations. Philadelphia: J. B. Lippincott Company, 1941. Price, $6.00.

The New International Clinics, Volume 2, New Series 4, June 1941. Edited by GEORGE MORRIS PIERSOL, M.D., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, Philadelphia, with 17 Collaborators. Pp. 299; illustrated; 1 colored plate. Philadelphia: J. B. Lippincott Company, 1941.

A wide range of subjects is covered in this number. Several "clinics" are presented from Yale and from three Lexington institutions. The "Review of Recent Progress" is on Chronic Gastritis, though the first article, on "The Functions of the Adrenal Glands" is also a digest (13 pages).

Proceedings of Meetings of the New York Pathological Society held Nov. 30 and Dec. 28, 1939, and Jan. 25, Feb. 29, March 28, April 25, and May 23, 1940. (Reprinted from the Archives of Pathology, March, June, August, September, and October, respectively, 1940.) Pp. 39.

Prostata-Krebs wie Paraprostata-Hypertrophie sind Folgen hormonaler Störungen, die wir je früher je besser beeinflussen können. 13 Jahre hormonale Krebs-Prophylaxe wie auch hormonale Behandlung der Paraprostata-Hypertrophie bei mehr als 1000 älteren Menschen. By DR. MED. PAUL NIEHANS, Chirurg und Urologe F. M. H. der Klinik von Clarens und der Spitäler von Vevey und Montreux (Schweiz). Pp. 48. Bern: Hans Huber, 1940.

NEW EDITIONS.

The Principles and Practice of Ophthalmic Surgery. By EDMUND B. SPAETH, M.D., Professor of Ophthalmology in the Graduate School of Medicine of the University of Pennsylvania, Philadelphia; Attending Surgeon, Wills Hospital, etc. Pp. 886; 451 engravings containing 1149 figures and 6 colored plates. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1941. Price, $10.00.

Dietetics for the Clinician. By Late MILTON ARLANDEN BRIDGES, B.S., M.D., F.A.C.P., Director of Medicine, Detention, Rikers Island and West Side Hospitals, New York; Consulting Physician, Seaview Hospital, Staten Island, N. Y.; and Department of Education, New York University, New York, etc. Pp. 960. Fourth Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1941. Price, $10.00.

Clinical Aspects of the Electrocardiogram including the Cardiac Arrhythmias. By HAROLD E. B. PARDEE, M.D., Assistant Professor of Clinical Medicine, Cornell University Medical College; Associate Attending Physician, New York Hospital; Consulting Cardiologist, Woman's and Methodist Hospitals, etc. Pp. 434; 219 illustrations on 102 figures. Fourth Edition, revised. New York: Paul B. Hoeber, Inc., 1941. Price, $5.75.

Fractures and Other Bone and Joint Injuries. By R. WATSON-JONES, B.Sc., M.Ch. ORTH., F.R.C.S., Civilian Consultant in Orthopædic Surgery of the Royal Air Force, etc. Pp. 724; 1034 illustrations. Second Edition. Baltimore: The Williams & Wilkins Company, 1941. Price, $13.50.

Synopsis of Diseases of the Heart and Arteries. By GEORGE R. HERRMANN, M.S., M.D., PH.D., F.A.C.P., Professor of Medicine, University of Texas; Director of the Cardiovascular Service, John Sealy Hospital; Consultant in Vascular Diseases, U. S. Marine Hospital. Pp. 468; 91 illustrations. Second Edition. St. Louis: The C. V. Mosby Company, 1941. Price, $5.00.

Foundations of Neuropsychiatry. By STANLEY COBB, A.B., M.D., Bullard Professor of Neuropathology, Harvard Medical School; Psychiatrist in Chief, Massachusetts General Hospital. Pp. 231. Second Revised and Enlarged Edition of the Work formerly known as A Preface to Nervous Disease. Baltimore: The Williams & Wilkins Company, 1941. Price, $2.50.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
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CHRONIC CONSTRICTIVE PERICARDITIS.

THERE has been much confusion in the use of the term adhesive pericarditis. Adhesions of the visceral and parietal pericardium may or may not interfere with cardiac function and therefore may or may not produce symptoms. In one autopsy series[46a] of 144 patients with partial and complete adhesive pericarditis only 57 (39.5%) presented complaints which made the heart the major issue in the clinical picture, and 47 of these had associated heart disease, leaving 10 with an adherent pericardium alone. Of the 47 with associated cardiac disease, 25 had rheumatic heart disease with aortic or mitral lesions or both. Adhesions vary from a few thin strands connecting the visceral and parietal pericardium to complete obliteration of the cavity, as well as external adhesions to the pleural and mediastinal structures—so-called mediastino-pericarditis.

Adhesive pericarditis may be classified into two varieties, that with constriction of the heart and that without. The non-constrictive variety may show partial or complete obliteration of the pericardial cavity as well as mediastinal adhesions. Symptoms arise in such patients upon two bases. The first is associated heart disease, which occurs frequently as stated above. In such patients the cardiac symptoms and signs are almost invariably produced by the associated disease. This is true, for example, in rheumatic heart disease. Associated adhesive pericarditis, although produced by the rheumatic fever as the result of more acute forms, consists of light non-constricting adhesions which for the most part give few or no symptoms. The second is tugging and pulling on mediastinal structures by adhesions. This, if it produces marked angulation or torsion of the heart, could produce hypertrophy of the heart, obstruction to inflow and similar changes.

There has been much dispute in the literature concerning the effect of non-constricting adhesions alone, without associated heart disease, upon the heart size and the production of cardiac hypertrophy.[24,26,32,37,39] In some reports, hypertrophy is recorded; in others none was found

at all. Armstrong[1] has adequately reviewed this subject. With adherent pericardium as the only cardiac disease one autopsy series[46a] showed a widely varying heart weight with marked increases in certain instances. No instances of hypertrophy have been reported in several similar series. Hosler and Williams[26] believe that adhesions *per se* do not cause circulatory embarrassment unless extensive enough to cause cardiac compression. They found no instances of hypertrophy in the presence of extensive pericardial adhesions unless associated disease was present. In 76 patients the only instances of hypertrophy with pericardial adhesions occurred in 54 patients with assignable cause. In Smith and Willius[46a] series coronary sclerosis and rheumatic heart disease were present in slightly over 21% each, and hypertension in 17.4%. Beck[3a] does not believe that adhesions play a rôle in heart failure, cardiac dilatation or hypertrophy. Both his clinical and experimental evidence supported the view that non-constricting adhesions were silent and incidental unless they produced twisting or angulation. Such adhesions form the picture which is often seen at autopsy when not at all suspected during life. Further evidence that complete adhesions between the two pericardial surfaces of and by themselves do not necessarily interfere with function to an important degree has been obtained by the deliberate production of adhesions by the introduction into the pericardial cavity of such materials as magnesium silicate or talc[48] and carborundum sand[23] to establish collateral circulation for coronary disease. This has been done in experimental animals, and, with talc, in humans without the development of cardiac embarrassment. The adhesive pericarditis of rheumatic heart disease falls into this class. Rheumatic fever, although it produces acute fibrinous pericarditis and pericarditis with effusion, eventuates in adhesions which are not thick, dense and constricting. Such changes may involve surrounding tissues at times drawing upon the mediastinal structures and chest wall.

The adherent pericardium, when thickened and constricting produces at times a typical and dramatic clinical picture, Chronic compression results from a variety of anatomic lesions,[3a] for example, pericardial effusion, scar, and neoplasm, or a combination of these. A thickened contracting pericardium which may or may not be adherent is the usual cause. Beck has seen the picture produced by intermittent hemorrhage from sarcoma involving the pericardium, and some[10] believe that a fibrous pericardium may interfere with cardiac function in patients with marked hypertrophy. The remaining remarks will be devoted to chronic constrictive pericarditis resulting from a thickened fibrous pericardium.

An historical review of chronic constrictive pericarditis has been given by White[51a] and will not be repeated here. The term is applied, as stated above, to pericardial disease, producing a thickened unyielding coat which interferes with diastolic filling of the heart. Pick[42] gave the name pseudocirrhosis of the liver to the disease, which in his patients included not only mediastinopericarditis but polyserositis and chronic inflammation of the pleura and peritoneum. Many terms have been applied to the disease. Besides Pick's disease, chronic constrictive pericarditis and pericardial pseudocirrhosis of the liver, these include adhesive pericarditis, chronic obliterative pericarditis, concretio peri-

cardii, symphysis cardiaca, mediastino-pericarditis, Concato's disease and polyserositis. The use and abuse of some of these terms has already been given. More will appear as the discussion progresses.

Etiology. In many instances the cause of chronic constrictive pericarditis rests upon unknown grounds. From what has already been said, rheumatic fever is not under suspicion. None of White's 28 patients had rheumatism and that is the experience of others.[1] There are, however, a number of reported patients[49] in whom a history of rheumatism has been obtained. However, it is difficult to evaluate the term in the light of rheumatic fever. In several instances where such a history has been obtained the autopsy findings in the heart did not bear out the presence of rheumatic valvulitis.

Many possible etiologic agents have been considered. These include tuberculosis, syphilis, pericardial trauma,[18] and pyogenic involvement of the pericardium directly from the lung or by metastasis from foci of infection, for example, by streptococcus,[36] pneumococcus,[12] and staphylococcus.[8,30] The development of chronic constrictive pericarditis from acute inflammatory pericarditis produced by such infections has not been well understood, because of the long periods between the clinical pictures at times. The number of patients followed through in this way is increasing. In several reported instances also, pus pocketed in the constricting pericardium has shown the offending organism.[8,30]

Tuberculosis is definitely known to produce the picture[1,22] even though by the time the chronic stage is reached there is often doubt in the diagnosis. In Burwell and Blalock's group of 19 patients,[5,7] 16 were considered to have tuberculous pericarditis, and in 11, tubercles were demonstrated microscopically. This is the only report with an appreciable incidence of tuberculosis. Others have obtained strikingly different figures.[1,3a,31,51a,b] Beck says that about 10% are tuberculous.

Purulent pericarditis is known to eventuate in chronic constrictive pericarditis. In the past operative intervention for purulent pericarditis has been condemned because of the frequent complication of obliterative pericarditis.[45] However, Shipley and Winslow's reports[45,52] include 39 cases to support the opposite view that fatal obliterative pericarditis is not the inevitable outcome. After 1 to 32 years, 35 patients were alive, well, and working as usual. Two (5.13%) had pericardial symptoms.

Purulent pericarditis[45] in most cases is attributed to metastases from foci of infection, such as osteomyelitis and other suppurative processes, especially pneumococcal, staphylococcal and streptococcal. Occasionally purulent pericarditis results from bullet and stab wounds. Purulent pericarditis tends to cause local adhesions anteriorly because the heart is said often to be against the anterior wall of the sac. In Shipley and Winslow's case the exudate had pushed the heart forward into juxtaposition to the pericardium, producing adhesions.

Many instances of chronic constrictive pericarditis cannot be traced back to acute pericarditis of known etiology. In only half of Smith and Willius's series of 144 patients with pericardial adhesions were causes found for the changes seen.[46a] In the 28 patients of White's series[51b] the etiologic agent was unknown in most instances.

Age incidence varies through a wide range. In White's series

again onset of the disease was noted from $5\frac{1}{2}$ to 51 years. Only 5 patients were beyond the age of 40. Others have seen older patients but in general it is primarily a disease of children and young adults. Males are more often affected than females in a ratio of about 3 to 1 down to 2 to 1. It is interesting to note that the sex ratio, males to females, in purulent pericarditis was $2\frac{1}{2}$ to 1 in 73 instances,[45] a strikingly similar figure which again tends to associate purulent with constrictive pericarditis.

Pathology. No attempt will be made to cover thoroughly the pathologic aspects. The acute processes already mentioned above may progress to a chronic stage with thickening, fibrosis, calcification and constriction. The heart cannot relax sufficiently in diastole. As Sprague[47] states, the heart chambers are fundamentally normal but blood is prevented from entering them because of interference with the capacity of the chambers to dilate and receive blood because of the inelastic armor of the thickened pericardium. Complete adhesions of the visceral and parietal layers are not necessary but are the rule. One or the other layer or both may be chiefly responsible. This fibrosis may be localized or diffuse. The type of fibrous tissue differs from that seen in non-constrictive adhesive pericarditis.[1] It is thicker and denser with considerable hyalinization. The anterior surface is usually the area most involved, and pocketing of fluid which at times contains the causative organism occurs. Adhesions to the chest wall may be a part of the pathologic picture but are not a part of the clinical picture.

Calcification occurs in a variable number of cases, according to White,[51b] about one-third. Definite descriptions of calcified pericardium go back 200 years.[12] In 1924 Turner[49] in thoroughly reviewing the literature found some 89 cases and added 3 of his own. The diagnosis has been a rarity in the past but with frequent use of roentgenograms is becoming more and more common. A large number of known cases are not reported also. It is more often absent than present, in constrictive pericarditis and may occur in adhesive pericarditis without constriction.[1] It was present in 10.4% of 144 cases[46a,b] having adhesions of all degrees. In Jones' collected group of 56 patients with calcified pericardium,[28] he found 5 with a history of acute rheumatism, 5 with vague rheumatic pains and 11 where absence of a history of rheumatism was absolutely stated.

The cause of calcification is obscure. It is said to occur in dead or dying tissues and in inspissated exudates. Wells[50] made these statements in this journal in 1902. To him it seemed that calcification of adhesions was not common, and in his group of 4 patients calcification of inspissated exudates seemed more likely in such infections as the pneumococcus produces rather than in tuberculosis. Others[46a] also believe that calcification is the end-result of inflammatory disease, more particularly that which is non-tuberculous. Hemorrhage into the pericardium is given as a cause of calcification.

The effects of adhesions upon heart size have already been discussed. The compressed heart of constrictive pericarditis is a "quiet" organ.[3a] It cannot dilate and receives too little blood so that it puts out too little blood. Beck believes that such a heart can and does undergo atrophy of disuse with reduced work.

The relationship of polyserositis, so-called Concato's disease, to con-

strictive pericarditis is not clear. Constrictive pericarditis may occur with or without polyserositis and polyserositis with or without constrictive pericarditis. The two frequently occur in the same patient. Polyserositis is occasionally found in young individuals due to tuberculosis or associated with pneumonia or unknown cause.[51b] The perihepatitis and perisplenitis, so-called frosted or iced liver and spleen, are regarded as part of a chronic peritonitis. The process, presumably infection, has associated with it exudation in the serous cavities, pleura, pericardium and peritoneum.

The work of Beck[4] suggests that there may be a more close association between the iced liver and constrictive pericarditis than has been supposed. He produced chronic constrictive pericarditis in animals experimentally and found present in the abdomen of some of his animals changes in the liver associated with a fibrinous exudate not associated with infection, and presumably due to venous stasis. The question arises whether the process, had the experiment gone long enough, would have produced a sugar coating.

Clinical Aspects. Subjective symptoms are usually of little importance. Dyspnea may be present on exertion but the patient may lie comfortably on the back. Weakness, ease of fatigue, cough, anorexia, epigastric distress and swelling are frequent. There may be no symptoms referred to the heart at all. The obliteration of the pericardial cavity with or without calcification may not cause sufficient constriction to produce symptoms or striking physical signs, and the diagnosis will turn up as a surprising one at autopsy when not at all suspected during an active life. Even when producing symptoms the evidence pointing to serious heart disease is meager. Epistaxis is not uncommon. Symptoms may be absent until introducing a progressively down-hill course or may be present and remain constant or vary through a certain range for years, thus producing chronic invalidism.

The symptoms and signs occurring in chronic constrictive pericarditis have their basis in a mechanism entirely different from that of congestive heart failure and hence recognition is important because of the differences in prognosis and treatment. This mechanism is well shown in the hemodynamic studies which have been carried out by Burwell and his associates,[7,8,9] by Beck,[3a,4] and by Heuer and Stewart.[25] Congestion results from an inability of blood to enter the heart through inadequate diastolic filling rather than because of myocardial weakness as in the usual types of congestive heart failure. The heart therefore puts out less blood per beat. Measurement of the circulatory constants by the groups mentioned above shows an increased arteriovenous oxygen difference, an elevation of venous pressure, prolongation of the circulation time and diminution of the cardiac output per minute, stroke volume, and cardiac index (cardiac output in liters per square meter of body surface per minute). The total blood volume is increased.

These findings fit in well with the concept of constriction and "inflow stasis." The heart muscle is efficient and the valves not diseased, but there are reduced excursions of the heart and with exercise tachycardia is necessary to compensate for the inability to increase the stroke output. There are no remarkable murmurs. This has led Beck to include: 1, a relatively small quiet heart with, 2, high venous pressure, and 3, ascites and enlarged liver, as the triad of findings in chronic

cardiac compression. With compression and inflow stasis the venous pressure becomes elevated, followed by the results of venous stasis, as cyanosis, ascites, enlarged liver and spleen, edema, varicose veins, and hydrothorax. Cirrhotic changes in the liver develop with prolonged stasis. Burwell and Blalock[7] point out that the high venous pressure is persistent and although it fluctuates it does not return to normal as in congestive heart failure. Intravenous infusions affect it as they do the venous pressure in congestive heart failure, with a rise in the pressure at a rate which causes no rise in normal individuals. As one would expect with reduced cardiac output systolic blood pressure is lowered as is the pulse pressure. In inspiration the blood pressure may fall, producing a paradoxical pulse. With the cardiac output per beat fixed, exercise results in excessive tachycardia.

Cyanosis of varying degrees occurs. Its mechanism has been studied by Castex, Capdehourat, and Mazzei,[10] who found that it depended upon the increased arteriovenous oxygen difference produced by an increased removal of oxygen as a consequence of slowing of the arteriocapillary circulation.

Frequently there is rather marked ascites with very little and even no peripheral edema. This is not invariably true and there are patients with marked edema of the extremities. There are several reported instances[15] of edema of the head and neck appearing overnight and disappearing after the patient is up and about for several hours. An adequate explanation for the discrepancy between ascites and peripheral edema is lacking. Variations in the relative increase in pressure in the hepatic veins and the inferior vena cava,[51b] and proper relationships anatomically of the hepatic veins for stasis especially with involvement of certain parts of the pericardium,[32] have been advanced as possible explanations.

There are additional cardiac findings of interest. The heart is never markedly enlarged unless there is some complicating disease. Likewise, there are no important murmurs unless, as occasionally happens, there is some other form of heart disease present.[51b] The cardiac rhythm is usually regular but auricular fibrillation is not uncommon. Smith and Willius[46a] found auricular fibrillation in 8 (80%) of 10 patients with adherent pericarditis unassociated with other types of heart disease. French authors[43] give the incidence as 33% in chronic constrictive pericarditis. In White's series auricular fibrillation occurred in 6 of 28. Paradoxical pulse occurs in varying degrees and in some series the incidence has been high. Broadbent's sign[51a] is not seen.

A most interesting finding, with calcification, is the presence in the protodiastolic time interval of a sound which Lian, Marchal and Pautrat[33] called a protodiastolic pericardiac vibration. It is best heard at the apex or over the body of the heart. The sound occurs at the time of the physiologic third heart tone and protodiastolic gallop but differs in character.[53] In place of the dull thud one hears a sharp vibrating sound which is much higher in pitch. Its mechanism is not understood. Perhaps impact of the heart against surrounding structures is important.[53] How the calcium enters in its production is not clear. South American investigators[2] taking sound tracings and simultaneous phlebograms have shown that it starts after the top of the *V* wave during the rapid inflow phase. By such relationships it can

be distinguished from the opening snap of mitral stenosis, gallop rhythm and the physiologic third heart sound.

A summary of the literature on the electrocardiographic changes in constrictive pericarditis has recently been published by Noth and Barnes.[38] Electrocardiograms usually show low and slurred complexes and *T*-wave inversion simulating that of coronary disease. There may be slight right or left axis deviation and of course auricular fibrillation is not uncommon. All of these findings in whole or part may persist after operative cure. The Dieuaide test,[14] which measures the change in electrical axis of the electrocardiogram with change in position of the body, has been advocated in the past as an index of fixation of the heart. Fixation by adhesions, it was thought, would prevent motion and, besides detection by physical or Roentgen ray examination, the electrocardiogram would show no or little change with the patient on the right and left side. It has been shown, however, that with constrictive pericarditis even with mediastinal adhesions the heart may be mobile, and when the heart is fixed the change in relationships to surrounding structures may account for changes in the electrocardiogram. Also in certain persons without adhesions especially with greatly enlarged hearts there may be no change with body shift.

Roentgen Ray Findings. The Roentgen ray may show normal findings in some instances, but usually is an important aid in diagnosis. Lipiodol has been used to visualize the pericardial sac experimentally in animals[34] but it is not attempted in diagnosis in humans. The Roentgen ray diagnosis of chronic constrictive pericarditis has been discussed in detail by Freedman.[17] Fluoroscopic examination is invaluable because of recognition of respiratory changes in position and contour of the cardiac shadow and diaphragm. The fixation of the heart and thickening of mediastinal structures may be seen. Pulsations may be diminished and at times the borders hazy. Kymography is valuable in recording cardiac excursions as first shown in this country by Johnson[27] and may be used to follow the progress of such patients postoperatively.[19] Freedman points out that in the Roentgen ray investigation of suspected cases the most conclusive sign is calcification. Lateral views may be necessary for its detection and such shadows by position may indicate the pericardial thickness, which may reach 1 to 1.5 cm. The cardiac configuration shows no or little enlargement and characteristically a triangular shaped heart. Other contours are found, however.

In summary, the chief points in the clinical picture of chronic constrictive pericarditis have been outlined by Sprague[47] as follows: 1, The patient is usually a child or young adult. 2, Ascites and hepatomegaly appear insidiously and often are out of proportion to peripheral edema. 3, Venous pressure is elevated, often to three or more times normal. It remains elevated without fluctuations seen in congestive heart failure. Femoral venous pressure may be reduced somewhat by abdominal paracentesis. 4, Dyspnea may occur on exertion but in the absence of pleural fluid orthopnea is present. 5, Cyanosis consistent with venous engorgement is present and may be intense. 6, Heart size is usually normal but moderate enlargement may be found. 7, The heart is free from murmurs of significance. Auricular fibrillation may be present. 8, Blood pressure and pulse pressure are low. Paradoxical pulse is common. 9, Broadbent's sign is absent. 10, Pleural effusions are

common. 11, Roentgen ray findings include calcification of the pericardium, limitation of cardiac pulsation, or limitation of pulsation of the right border, dilatation of the superior vena cava, dilatation of the auricles, prominence of the left upper border, and pleural thickening. Still the examination may be essentially negative. 12, Electrocardiographic findings include low voltage and inverted *T* waves of the coronary type.

Diagnosis. Importance of proper diagnosis and differentiation from the usual types of congestive heart failure lies in the entirely different form of treatment, and the good prognosis following the success of operation. There is no pathognomonic sign and one must seek out all available findings by all methods of examination, history, physical examination and laboratory.[51b] The history of previous acute pericarditis, either wet or dry, is helpful but such a history is not always obtainable. On occasion the development of the picture from acute pericarditis is seen by one observer. The development of the clinical picture already described above, especially the evidences of congestion with increased venous pressure, hepatomegaly, ascites and little clinical evidence of heart disease on examination of the heart itself, should lead to further investigation for the important findings already given to establish the diagnosis. Other conditions producing interference with venous inflow to the heart as well as other causes of edema and ascites must be ruled out. These include congestive heart failure, polyserositis, cirrhosis of the liver and simulating lesions, inferior vena caval syndrome, and nutritional edema.

The localized hemodynamic changes of cirrhosis of the liver should clearly differentiate it. However, atrophic cirrhosis of the liver may be found associated with constrictive pericarditis. The same confusion which occurs in differentiating cirrhosis of the liver might cause difficulty with Chiari's syndrome (thrombosis of the hepatic veins), which produces a large liver, ascites, with rapid reaccumulation following tapping, as well as a number of other findings.[29]

The inferior vena caval syndrome may be confused with constrictive pericarditis for reasons similar to those above. A normal heart would be expected. Recently there has been reported a patient[20] with autopsy proof of inferior vena caval obstruction showing rapidly recurring ascites, paradoxical pulse, increased venous pressure in the upper extremities as well as in the lower extremities, together with electrocardiographic changes characterized by low complexes.

Nutritional edema usually presents a satisfactory history, lowering of the blood protein, normal venous pressure, a clinically normal heart and liver, and ascites that is not as prominent as in constrictive pericarditis. Another nutritional state which could possibly cause confusion is beriberi, since minimal findings are found over the precordium with enlarged liver, peripheral edema, and ascites. However, the history together with evidences of polyneuritis, absence of evidence of cardiac constriction, and the reaction to treatment should make the differentiation a simple one. Beriberi heart without polyneuritis has been reported.[13]

Remarks concerning polyserositis have already been made and will not be repeated. With both diseases present simultaneously, the picture is confusing. Evidences of infection, the clinical aspects already described, and the differentiation of transudates and exudates is of

importance. It appears that pericardial fluids in the absence of inflammation may contain large amounts of protein,[35] and although ascitic and pleural fluid in transudation is poor in protein, it is not always easy to differentiate transudates and exudates.

Other cardiac states with congestion must be ruled out, particularly mitral and tricuspid stenosis. The rarity of tricuspid disease and the frequency of its association with mitral stenosis is helpful particularly if the mitral disease is evident. Tricuspid stenosis has many circulatory changes in common with chronic constrictive pericarditis.[7] The circulatory changes rest upon an inability of blood to enter the heart, elevated venous pressure and its effects become evident, and digitalis and rest are not very helpful, because of the mechanical rather than myocardial disturbance. Mitral stenosis usually offers but little difficulty. The diastolic murmur is not seen in constrictive pericarditis, but, despite different characteristics, the protodiastolic pericardiac vibration has been confused with it. Congestive heart failure may make the murmur of mitral stenosis difficult to hear and enlargement of the heart may displace it from the usual area of auscultation. Auricular fibrillation occurs in both. However, the heart may be greatly enlarged in mitral stenosis, axis deviation in the electrocardiogram may be extreme and other evidences, such as fluoroscopic examination may help clear up the confusion when it does exist.

Prognosis. The prognosis for life varies greatly. In those developing symptoms of cardiac constriction, although the disease has obviously been present for a long time in an extremely active individual without any complaints, the course may be rapidly down-hill with death in some months. The disease is compatible with a long life, but activity may be impaired to a mild or marked degree making the individual a chronic invalid, subjected to periods of bed rest, even hundreds of abdominal paracenteses, and continual control of activities. With surgical treatment to relieve the constriction, however, if the diagnosis is adequate and if complicating disease is absent, cure may be dramatic and startling. A chronic invalid may again become a normally functioning individual. This is, however, not a blanket statement. In White's series, 11 of 28 were functionally cured by surgery. In Churchill's 37 collected cases[11] with decortication, of 32 there were 19 (59%) with excellent results. The mortality rate was 21.8%. Schmieden and Westermann[44] report 6 of 22 patients (27.3%) with full recovery, 6 (27.3%) markedly improved, 1 (4.5%) who died at operation, 7 (31.9%) who died postoperatively and 2 (9%) who died after transitory improvement. Some of these patients are duplications of the above series. Churchill's patients are included in the group reported by White.[5,15] Heuer and Stewart[25] reviewed the literature on the surgical treatment and found, as the above figures show, that although results from operation are striking, primary mortality of decortication of the heart is still high (33%), a value comparable to that of Harrington and Barnes.[21] Of 143 cases in the literature exclusive of their own, 19 died on the operating table and 28 in the immediate postoperative period, 32.8% of the entire number, and of 135 with available data, 54 (40%) died during or soon after the operation. All of their 7 cases recovered. Of 143 there were 50 (36.6%) cured and 25 (17.4%) improved. Immediate effects, that is for several months, were striking although it may

take up to a year for full benefit to be obtained. Cures up to 18 years are on record and many patients have remained well for 2 to 3 years or more. Paessler,[41] in an investigation of 71 cases, concluded that late results were not as favorable as early ones seemed to promise. He believes that improvement has in an appreciable number of cases been followed in some years by ill-health with a variety of manifestations not representing constrictive pericarditis, and he suggests that chronic constrictive pericarditis is one manifestation of a general process and that operation may not be sufficient for cure.

The high mortality appears at first to be striking, but in an incapacitating and fatal disease, improvement or cure of 60% of the patients subjected to surgery is an important record.[35] Also only 8 surgeons at the time of Heuer and Stewart's report in 1939 had operated on 5 or more cases, and it is expected that with better diagnosis and selection, with improvement in care and with added experience the results will improve. Benefit from surgery is to be expected only when constriction is the cause of the symptoms and when other causes of cardiac disability are absent.

Eliason and Brown[16] point out that it is impossible to conceive of a pericardiectomy wound healing after constrictive pericarditis without adhesions tending to fix the heart to the sternum and surrounding structures. But these adhesions, unlike the thickened constricting ones removed, are apparently of no clinical importance. It has already been stated that adhesive pericarditis without angulation or constriction of the heart gives no important symptoms. Postoperative adhesions clinically, at autopsy, and at other operations[36] have been seen to produce nothing in the way of disability of the heart. In some of the patients the follow-up is not sufficiently long to ensure the absence of such a complication.

Treatment. Many factors concerned in treatment have already been given and will not be repeated. Medical treatment has little fundamental effect and is temporary. Venous pressure is not reduced to normal. Rest is helpful, but with return to exercise, the condition is aggravated and the symptoms and signs again become worse. The patient is a semi-invalid or at times is completely bedridden. Measures effective in other types of edema are helpful, for example, restriction of fluid and salts, the use of diuretics and paracentesis. Diuretics, particularly the organic mercurials, are useful and have benefited patients over long periods of time when operation has not been considered, as well as to prepare the patients for operation. Abdominal and thoracic paracenteses are helpful and often necessary procedures in preparation for operation and in carrying the patient along if operation is not done. Abdominal tapping has been done once or twice weekly for even hundreds of times.

Digitalis is not advocated by many authorities. Improvement with its use is not striking and the mechanism of production of symptoms shows why. If it reduces the pulse rate without the heart being able to compensate in its output by an increased stroke volume of blood, circulatory embarrassment would increase. With a fixed output per beat the only way the heart can increase its output per minute is by increasing the rate.[7] Reducing the rate would be unfavorable if it dropped below the optimal level. However, it is stated[7] that pre-

operative digitalization may be advisable, for the underworked heart which has atrophied is suddenly burdened with increased work at operation and might be usefully supported by digitalis. European workers[44] have used strophanthin in the same way. With auricular fibrillation digitalis may be beneficial.

For the surgical treatment the interested reader is referred to the recent reviews of the literature by Heuer and Stewart,[25] Beck,[3b] and Harrington and Barnes.[21] Details of preoperative preparation, operative procedures, anesthesia and postoperative care may be found there. Remarks on preoperative bed rest, restriction of salt and fluids, use of diuretics and digitalis and paracentesis have already been given.

The actual operative procedure consists of a Delorme decortication of the heart. Churchill[11] was the first to do this operation in this country and was followed by Beck[4] and others until it is done quite extensively today. Resection of the adherent thickened pericardium is done and the excellent results already given above are obtained when constriction as evidenced by small pulse, increased venous pressure, small heart and other findings already mentioned are the cause. The cardiolysis of Brauer[6] which consists of removal of some of the rigid parts of the thoracic cage to permit a retraction of the chest wall when the heart is adherent to it, relieves tugging and would be important if such tugging were important. It does not help diastolic filling from constriction, the main difficulty in chronic constrictive pericarditis.

Decortication does not always give an immediate dramatic change in the circulation in indicated cases. In Eliason and Brown's case, several days elapsed before improvement, which progressed slowly over several weeks and which in certain instances has continued up to a year. White[51a] noted a lapse of several days before diuresis begins and the same is true of Beck's patients[3a] in whom it has taken some days or weeks for venous pressure to drop and diuresis to take place.

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PEDIATRICS

UNDER THE CHARGE OF
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DIABETES MELLITUS IN INFANCY AND CHILDHOOD.

Many diseases have been rendered less hopeless by the developments of diagnostic and therapeutic improvements. To many physicians, especially those whose professional life antedates the end of the first decade of the present century, the diagnosis, treatment and, consequently, the prognosis of certain diseases are at a total variance with the teaching of these conditions when they were medical students. In no disease has there been a more complete change than in diabetes, especially in childhood. In the 1909 edition of his "Diseases of Infancy and Childhood," Holt[32] devoted a scant 2 pages to the consideration of diabetes mellitus. The following is his introductory paragraph: "In this chapter will be attempted only a description of the peculiar features which diabetes presents when affecting young patients. It is a very infrequent disease in children. Of 1360 cases of diabetes collected by Pavy, only 8 were under 10 years of age. In a series of 700 cases collected by Prout, only 1 case was under 10 years of age. In a series of 380 cases collected by Meyer, only 1 case was under 10 years of age." His discussion of prognosis is also of so much interest in comparison with prognosis now that this paragraph is quoted: "In few diseases is the prognosis so bad as in diabetes in children. So high an authority as Senator declares that diabetes in children is hopeless and all treat-

ment is useless. From a study of 77 cases, Stern reaches the same conclusion. There are, however, cases on record in which recovery is believed to have taken place. The cases that I have seen have all terminated unfavorably. In a given case the prognosis, as to the duration of the disease, is rendered much worse by the presence in the urine of diacetic and oxybutyric acids. This condition is even more serious than is a high percentage of sugar; that the patient will then live more than 3 months is highly improbable."

In his 1919 edition, Kerley[14] stated "True diabetes in children is, fortunately, a comparatively rare disease." Under the heading "Duration of the Disease" he stated, "Few cases live longer than a year. The majority of the cases terminate fatally in from 3 to 6 months." Under "Prognosis" he stated, "All my cases died within a year after the diagnosis was made. True diabetes is a fatal disease in children."

In his 1919 edition, Griffith[10] gave a slightly more optimistic outlook when he said, ". . . . The final prognosis in children is very unfavorable, if care is taken to exclude from the list cases not certainly diabetes, such as instances of transitory or alimentary glycosuria. Yet under newer methods of treatment the prognosis does not appear to be so uniformly bad as was formerly considered to be the case, and it would appear, as pointed out by Reisman and others, that the disease at this time of life may sometimes run a mild course and terminate in recovery."

The early advances in the treatment of diabetes are attributed by Garrison[8] to the dietetic studies of von Noorden (1895–1911), the extensive studies of Graham Lusk (1898–1915), F. G. Benedict and Joslin (1910–1915) and the effects of the fasting treatment of F. M. Allen (1915). While some improvement in prognosis followed the dietetic treatment, the most marked advances followed the introduction of insulin and the development of a combined dietetic and insulin treatment of this disease.

In 1923 following the introduction of insulin, Strouse[28] in Abt's "Pediatrics" ended a consideration of some length with the following prognosis: "In discussing prognosis of diabetes in children, scientific judgment must be tempered by philosophical understanding of the difficulties of accomplishing the very exacting conditions demanded by ideal treatment. A purely scientific prognosis might be given on a theoretical supposition that all conditions of treatment can be fully met. Under such conditions, for reasons already given in the body of this study, one can say with certainty that at present the diabetic child has a decidedly better chance than he had 10 years ago. With the improved method of treatment the average diabetic child today lives longer than he did in the past decade; and if it were possible to maintain ideal conditions for a long period of time in all diabetic children, it might be possible likewise to increase the span of life considerably more. Unfortunately, however, the life of such a child cannot be lived within the walls of an institution or under the constant control of authorities. At times of delicate balance in the metabolism, the diabetic child may have to go to school or play in the street with other children. Any normal contact of this child with the world submits him to the dangers of nervous influences (excitement or worry) which might easily be the straw to break the back of his metabolism. Any normal contact with a few pennies in his pocket, may bring him to

the corner store and its alluring display of cheap candy or cake. The sugar hunger is likely to overwhelm him, and a carbohydrate spree results. Many of the children whom I have seen with diabetes have gone into coma after such carbohydrate spree."

In the more recent literature there is a more optimistic attitude towards diabetes in the young. Although there has been improvement in the situation, the child diabetic has many pitfalls that may prove disastrous. Selander[23] followed a number of cases after they left the hospital and was able to obtain reports of 155 children out of 156 treated with insulin. Of these, 27 (17.4%) had died. The morbidity during the 5-year period from 1935 to 1939 did not show a decline in comparison with the preceding 5-year period. The cause was found in an increased mortality among the group over 16 years of age, which was more numerously represented in the last 5-year period. The duration of the diabetes among those who died during the period of 1925 to 1929 was 2.2 years on an average, during the period of 1930 to 1934 on an average of 4.5 years and during the period of 1935 to 1939 on an average of 7.4 years. Coma as a cause of death was found to have decreased during each 5-year period, while tuberculosis had taken the lead during the last period as the most frequent cause of death. There were no certain complete cures observed in any case of diabetes.

McDaniel, Marble and Joslin[16] studied the records of diabetic patients for the purpose of discovering any analogies between the cause of their diabetes and that produced experimentally in animals and to see if any patients could be found who seemingly were cured or had benefited by early energetic treatment. The records of those few patients were studied in whom at postmortem examination there were microscopic evidence of hydropic degeneration of the islet cells. Recent work has shown that at this stage of degeneration of islet tissue the process is reversible. The data showed that, although no cures can be claimed, early, vigorous treatment in certain patients with a restricted diet or insulin or both seemed to have brought about an unexpected degree of improvement. Many other patients, treated in a like manner, responded with only the expected improvement. Resting procedures, such as fasting, fat feeding and insulin, prevent the degenerative changes from occurring in cells not already affected and permit the restoration of those exhausted cells, which still retain the ability to recover. They feel that diabetes is never complete until death occurs as there are always some functioning islet cells and to keep them in a functioning state is the main goal of treatment. It is their policy to begin vigorous treatment with insulin and a low carbohydrate diet with the required calories made up in fat. If, after a few weeks, there were no signs of improvement they would increase the diet to one of moderate carbohydrate restriction, assuming that by this time all beta cells which could recover had done so. They would be extremely slow in reducing the insulin dosage and diligent in its use with intermittent infections. They believe that the diabetic patient should be taught to guard his islet tissue as he does his toes and limbs.

The presence of sugar in the urine is not necessarily evidence of the presence of a true diabetes. Bayer and Davis[2] stated that it is especially difficult to rule out diabetes in children. Since the variations of blood sugar in the normal child are so great, normal readings are not

always a guarantee of normal sugar metabolism. It is unfortunate to view too gravely a repeated glycosuria of dubious significance. They presented a series of cases which gives support to the optimistic outlook with regard to the prognosis of children with atypical glycosuria. Between 1923 and 1938 some 50 children passed through the pediatric ward of Stanford University School of Medicine with a diagnosis of possible diabetes mellitus. The glycosuria of 9 of the children was either considered non-diabetic or called diabetic with definite reservations on the part of the staff. In the spring of 1939, from 2 to 11 years after the original diagnoses were made, it was possible to recheck every one of these 9 patients. It was found that only 1 of them was diabetic.

Goettsch and Mason[9] reported a case of lead poisoning with glycosuria. They carried out studies on this patient which showed that the height of the blood sugar was consistently normal or lower than normal and that the urinary concentration of sugar remained relatively constant irrespective of the diet. The glycosuria persisted for 5 weeks, and the concentration of urinary sugar fell as convalescence progressed. The studies were compatible with the suggestion that the condition in lead poisoning should be classified as a renal glycosuria. This is supported by a survey of 8 cases of lead poisoning with glycosuria in children. In 5 of these cases, in which determinations were made, the blood sugar values were normal. In 3 cases, in which dextrose tolerance curves were obtained, the curves were not of the diabetic type.

The question naturally arises as to what are the normal blood sugar values in children. Rudesill and Henderson[22] made 288 blood sugar determinations by the Folin-Wu method on 144 non-diabetic children from 2 to 15 years of age. They made readings on both the fasting specimens and those made at 11 A.M. on the same day. They found that there was no practical difference in the blood sugar values. By the Folin-Wu method normal fasting blood sugar values in non-diabetic children was found to be from 70 to 105 mg. per 100 cc. They felt that the values for the normal amounts of fasting blood sugar was of the greatest usefulness in the study and treatment of diabetes mellitus. Since slowly acting insulins have come into general use, there are more often needed figures for normal limits as a guide in therapy. In order to know the normal blood sugar level in a child, the normal upper and lower levels must be known. The range of normal values can be safely considered to be between 50 and 110 mg. per 100 cc., but probably it should be placed between 60 and 100 mg. per 100 cc. since practically all values are found to be within these limits. Levels for children between 2 and 15 years of age had the extreme range of 52 to 115 mg. per 100 cc., but there were only 5 instances in 288 tests which did not fall between 70 and 105 mg. per 100 cc. While an occasional value may be reported as slightly lower or slightly higher than these figures, it is a comparatively rare exception since 98% of these readings were between 70 and 105 mg. per 100 cc. These observations also showed that blood sugar values determined $3\frac{1}{2}$ hours or longer after meals may be substituted for fasting blood sugar values in clinical practice.

McKittrick[17] made determinations of values for blood sugar for 73 normal newborn infants and 1 infant of a diabetic mother. During the first week of life low values were found. The lowest point was reached by the average baby on the third day. Values for blood sugar

above 40 mg. per 100 cc. were regarded as normal in the first week of life. During the second week the range was found to be from 60 to 120 mg. with the average between 80 and 90. During the first 2 weeks of life a gradual elevation of the level of blood sugar occurred, with a decrease in the spread of the maximum and minimum extremes. The blood sugar regulating mechanism of the newborn infant is unstable and undergoes an alteration towards greater stability during the first 2 weeks of life.

Diabetes is classed as one of the familial diseases. For this reason the children of diabetic parents are expected to inherit the tendency to have this disease. As far as the newborn is concerned the opposite state is sometimes observed during the neonatal period. Smyth and Olney[25] studied 19 infants born of women whose pregnancy was considered to have been complicated by diabetes. In 14 of the mothers glycosuria appeared only with gestation and was controlled by diet or by diet and the temporary use of insulin. This suggested that the glycosuria was from other causes than diabetes. Of the entire group, 11 gave birth to excessively large infants. The infant's blood sugar, even allowing for predelivery insulin, was low. In 2 of the infants projectile vomiting and cyanosis were striking features, and these were doubtless related to persistent hypoglycemia. The use of subcutaneous glucose was extremely valuable in carrying the infants through the critical period until an apparent adjustment was made. A follow-up of 1 patient showed a hyperinsulin-like sugar curve at the age of 4 years. The reports of postmortems of infants born of diabetic mothers vary. In some no hyperplasia of islet tissue has been found, and the hypoglycemia must be considered functional in type. In others, the finding of hypertrophy and hyperplasia of the islets of Langerhans explain the hypoglycemia. The relative macrosomia, advanced bone age and more mature genital tract suggest a pituitary effect. Complete endocrine pathologic study was reported but the interrelationship was best described as dysfunction. Perhaps some interrelationship will be found to account for the mild as well as the fatal hypoglycemia of the newborn infant.

Miller and Ross[18] stated that the belief is widely held that the hypoglycemia of newborn infants, whose mothers have diabetes, is the cause of the cyanosis, muscular twitchings, convulsions and occasionally the death of the infant. They question whether or not the hypoglycemia so frequently observed in these infants is as significant in the production of symptoms as is generally supposed. They stated that, without more facts than are at present available, a discussion of the effect of hypoglycemia on the newborn infant must be largely conjectural. There are two outstanding facts. Low concentrations of blood sugar are to be expected in infants of diabetic mothers, and difficulties seem to occur more frequently in these infants than in those whose mothers do not have diabetes. Occasionally they found low concentrations of blood sugars in infants who presented no abnormal findings in the neonatal period and whose mothers did not have diabetes. The average blood sugar concentration in infants born of diabetic mothers was significantly lower than in normal full term infants. However, the blood sugar concentration in some full term babies was as low as that of infants of diabetic mothers. In normal premature infants the blood

sugar readings were practically the same as those of infants of diabetic mothers. The low blood sugar level in normal infants did not, as a rule, produce symptoms as these infants seemed to adjust themselves to the low concentration.

Sisson[24] pointed out that the infants of diabetic mothers showed a high morbidity and mortality rate. He studied 65 consecutive cases of infants, whose mothers had diabetes. He remarked that such a group of infants was non-existent two decades ago before the insulin era. Women with diabetes either did not become pregnant or failed to give birth to a living child. Since the use of insulin the fecundity of the diabetic woman has increased greatly and the juvenile diabetic patient has reached the childbearing age. For these reasons there are increasing numbers of pregnant women with diabetes mellitus and consequently an increasing number of babies of diabetic mothers. Diabetic mothers still have a large number of miscarriages and stillbirths. There has been a great variation in the mortality rate and in some reports the rate has been as high as 40%. Another observation has been that these babies are unusually large so that they are frequently called "giant babies." There has been no evidence that the skeletons of such babies are larger than normal or that the babies develop into larger types. Another conception from previous studies has been that these infants are frequently born with hypertrophy of the islands of Langerhans. Recent work has shown that the majority of the infants studied have this condition, although it may also be found in normal infants. This series of 65 infants of diabetic mothers was divided into three groups. The first group consisted of 37 babies who were normal at birth and whose course during the neonatal period was uneventful. This group included a few infants who were somewhat sluggish in breathing and who had minor degrees of cyanosis, but who were not thought to be different from a great many babies usually regarded as normal. It was found that 35% of this group were born of mothers who had diabetes for from 10 to 20 years and that 78% of them were delivered by Cæsarean section. Also 86% were delivered between the eighth and ninth months of gestation. The second group consisted of 16 infants who survived but who presented definite major symptoms, which generally occurred directly after delivery. These symptoms were not uniform, but were primarily respiratory with depressed reflexes and difficulty in eliciting crying. These symptoms usually persisted for the first 24 hours and rarely lasted more than 2 days. Oxygen usually improved the condition but parenteral dextrose was without much effect. In this group of 16 infants 31% of the mothers had diabetes for from 10 to 20 years. About a third of the mothers showed definite signs of preëclamptic toxemia with elevation of blood pressure, edema and albuminuria. Cæsarean deliveries were made in 50% of this group and all were born between the eighth and the ninth months of gestation. None of these infants were of abnormal size. The third group consisted of 12 infants of diabetic mothers who died within the first 3 days of life. There was a great variation in the symptoms and there was no common cause of death. The mortality rate was 18%.

The question of heredity in the etiology of diabetes is one that has received a great deal of attention. Hildegarde Then Berg[29] in Munich has been making a study with a basic material of some 85,000 diabetics

among whom there were 411 pairs of twins. In 147 of these pairs she found that 46 were enzygotic and 87 were dizygotic, while the exact zygotic origin of two pairs was open to question. Twelve pairs were found not to have diabetes. A pair of twins was termed absolutely concordant if each twin of the pair was at the time of the examination suffering from a manifest diabetes mellitus with demonstrable excretion of sugar in the urine. If 1 twin, although not manifestly ill and passing normal urine, showed by the tolerance test that the insular system was unable to metabolize a tolerance test dose of twice 20 gm. of dextrose, the pair was termed concordant according to tolerance. A group called discordant according to tolerance was also distinguished. Among these the dextrose tolerance test of the twin who was not manifestly ill revealed a normal blood sugar curve, which, after fasting, was not above 120 mg. per 100 cc. This curve at its peak did not exceed 180 mg. per 100 cc. After 40 minutes in the second tolerance test with dextrose it showed no further rise, and finally, after 120 minutes, it returned to normal. Termed probably discordant were those twins who could not be examined because they had already died but who, according to the histories of their cases, appeared not to have been affected with manifest diabetes mellitus. According to this part of her study 17 pairs of enzygotic twins were absolutely concordant, 13 were concordant according to tolerance, 6 were discordant according to tolerance and 10 were probably discordant. Of the dizygotic twins 9 pairs were absolutely concordant, 9 were concordant according to tolerance, 32 were discordant according to tolerance and 30 were probably discordant. The author is thought to have proved on this large group of twins that diabetes mellitus was purely hereditary.

Fischer[7] stated that diabetes was rare in twins, especially in childhood, and that the opportunity to study the non-diabetic twin rarely presented itself. He claimed that his presentation was the first of this type to be described. It was expected that the non-diabetic twin would show a decreased tolerance for dextrose. She was studied 3 times. The first curve was obtained soon after the diabetes was observed in her twin. The second was made about a year later after an infection and showed a decreased tolerance for dextrose. This might have signified impending diabetes but on repeated examinations the urine showed no dextrose. The last curve was made some 3 years later and was normal. From statistics it might be expected that this member of the pair will manifest diabetes later although there has not been any evidence to the effect as yet other than a temporary decrease of dextrose tolerance after an infection.

Brown and Thompson[3] made a study on the data pertaining to body growth, intelligence, heredity, sex distribution and incidence of acute infections of 60 juvenile diabetic patients. The group of patients included in this study appeared to be typical of the juvenile diabetic population of Minnesota and apparently representative of the general child population of the state as regards socio-economic status, race and geographic distribution. While one-third of the patients reported having had some acute infection other than the common cold within 6 months of the onset of diabetes, the group, on the whole, was as healthy as the non-diabetic siblings except for acidosis and insulin reactions. Limited measurements of this group revealed no consistent

or peculiar deviations from the average in height. The diabetic children were significantly underweight only during the first 6 months of their disease. In contrast to the superior intelligence shown by Joslin's diabetic children, the intelligence of this group showed no deviation from the average and no significant deviation from that of the control group of non-diabetic children or from the average of Minneapolis children. There were no characteristic abnormalities in personality.

According to White[306] the search for clinical evidence of endocrine imbalance in juvenile diabetes has become imperative because the results of present-day physiologic research indicate that experimental diabetes is a disturbance of endocrine regulation. The importance of these investigations rests not only with the fact that from the combined data of the laboratory and the clinic the mechanism of diabetes may be explained and its cause and prevention indicated, but also with the possibility that a more nearly perfect form of treatment may be developed. She presented data on 1250 patients with juvenile diabetes. The onset of the disease had occurred prior to the age of 15 years. In this group, there were 177 patients who showed prolonged hypophyseal involvement. Of the 177 patients, in 176 the anterior lobe of the hypophysis was concerned. Of these, 9 showed evidence of hyperactivity and 168 had manifestations of hypoactivity. Among these patients were 94 dwarfs, 22 with Froelich's syndrome and 51 with signs of infantilism. Only 1 patient had signs and symptoms related to the posterior lobe of the hypophysis. None of the 1250 patients showed signs of deficiency of the thyroid gland, but 3 had signs of hyperthyroidism, 1 had possible adrenal disturbance and 28 had lesions related to the gonads. All presumably showed hypofunction of the pancreas, but 2 presented signs of hyperinsulinism in addition. Disturbances of the liver were noted in 65. This may or may not have been endocrine in origin. The juvenile diabetic patient showed evidence of a disturbed hormone balance. There was striking evidence of hyperactivity of the pituitary body in the pre-diabetic stage, followed by diminution of activity which in its most extreme form occurred in the diabetic dwarf.

The effect of a preceding injection of diabetic blood as compared with normal blood on the response of the rabbit to insulin was studied by de Wesselow and Griffiths.[5] The animals were starved 18 hours before the experiment. Inspection of the curves showed that after injection of 10 cc. of plasma obtained from 9 non-diabetic middle-aged subjects and 7 young diabetic patients, all but 2 of whom had been receiving insulin for some time, there was no appreciable alteration in the form of the blood sugar curve during the period following the injection of insulin. In the case of 16 elderly diabetic subjects with abnormally high blood pressure, the majority of whom were overweight and of whom only 3 were receiving insulin, it seemed that a preliminary injection of the plasma into the animals resulted in an early arrest of the fall in blood sugar after insulin. Associated with this premature arrest there was a very definite tendency for the blood sugar to be higher than the control values during the remainder of the experiment. This effect of a diminished fall and a more rapid restoration of the blood sugar after the injection of plasma of these patients was particularly evident in 6 of these 16 patients. During the second period of 30 minutes following the injection of insulin the blood sugar had already

begun to rise and after 60 minutes the average blood sugar exceeded the initial value. In these respects the curves obtained after injection of plasma were in sharp contrast to those of the first two groups of patients. The conclusion was that the blood plasma of some elderly, obese, glycosuric patients was found to diminish the hypoglycemic action of insulin in a manner closely resembling that observed by other workers with extracts of the anterior pituitary gland. They felt that the knowledge of the metabolic disturbances in diabetes would undoubtedly be considerably extended as the thesis that the anterior pituitary gland and the pancreas act antagonistically in the control of carbohydrate metabolism is developed. Any alteration in the balance of those opposed influences must lead to abnormal carbohydrate metabolism.

Aside from the dysfunction of the pancreas, the other endocrine glands participate in the metabolic disturbances of diabetes mellitus and complicated regulatory hormonal mechanisms, which are controlled by the vegetative nervous system, are present. In experiments on animals, true diabetes can be produced by injection of prehypophyseal hormones. Strauch[27] reported a very instructive case which throws light on the mutual relations between the hypophysis and diabetes mellitus. This patient was 17 years of age and had suffered from exhaustion, bad memory and retardation of growth for 2 years. Examination showed underdevelopment, flaccid musculature, and accumulation of fat, especially in the lower part of the abdomen, hips and thighs. The structure of the body was normal without any feminine traits and the patient was normal psychically. The internal organs were normal. The genitals were very small and axillary and pubic hairs were completely absent. Treatment was started with testicular preparations but resulted only in diminished exhaustion and improved temper. No improvement of the other pathologic signs could be obtained. Prehypophyseal treatment was then instituted. Within 1 month the pubic hair began to grow and the fat accumulations diminished in size. Within 6 months the patient grew 5 cm. and his school work improved considerably. Six months after the beginning of treatment, excessive hunger and violent thirst appeared and soon afterwards sugar and acetone were found in the urine. The patient complained of exhaustion, restlessness and irritability. On admission to the hospital a blood sugar value of 326 mg. per 100 cc., 4.8% of sugar in the urine and large amounts of acetone and diacetic acid were demonstrable. A typical precomatose condition with cardiovascular disturbances was present and could be controlled by administration of insulin and glucose. Within 2 weeks the urine became free of sugar and acetone and the blood sugar decreased to 150 mg. per 100 cc. with 8 to 10 insulin units per day. The author thought that the diabetes mellitus in this case was produced by the hypophyseal hormone which had been successfully administered for the dystrophia adiposo-genitalis. No suspicion of a preexisting latent diabetes was present in this case. Care should be taken in administering vitamins and hormones which are not indifferent and they should be used only where there is a definite indication. From this case it is seen that there is a close relationship between diabetes mellitus and the hypophysis.

Steiner and Newcomb[26] observed that the association of hyperthy-

roidism with juvenile diabetes mellitus brought about a striking change in the diabetic state. The effect of hyperthyroidism on carbohydrate metabolism was well illustrated in one of the cases of their series. Because of the family history it might be suspected that these changes were the result of a diabetic tendency or of latent diabetes activated by the hyperthyroidism. It cannot be denied that this may result, yet careful study and prolonged follow-up of these cases are necessary before a definite diagnosis can be made. Interesting improvement followed in dextrose tolerance after the patient was made to rest and was given a high calorie diet and iodine was administered. This improvement would not have occurred without the use of insulin if diabetes had been a complicating factor. The differentiation of diabetes and hyperthyroidism is sometimes difficult and the hyperthyroidism may be overlooked. For this reason it is a wise procedure to have the basal metabolism of every diabetic subject and every hyperthyroid case should have a sugar study. There is a great similarity of the cardinal symptoms of the two diseases. Polyphagia, polydypsia and the loss of weight and strength are common to both. Sugar is frequently found in the urine of patients with hyperthyroidism and hyperglycemia is fairly common. The mechanisms of glycosuria and hyperglycemia are different in the two diseases. Patients with hyperthyroidism have glycosuria, postprandial hyperglycemia, impaired dextrose tolerance, a low respiratory quotient in the fasting state and depletion of the glycogen of the liver. These suggest diabetes mellitus. There are other physiologic findings which aid in the differentiation. The utilization of sugar by the tissues is increased. The arteriovenous blood sugar difference is normal or increased in spite of an increased rate of blood-flow. After a carbohydrate meal the rise in the respiratory quotient is higher and the fall more rapid than normal. The fall in the level of inorganic phosphates of the blood is normal. This is caused by the formation of a hexose phosphate compound in the process of utilization of dextrose by the tissues. On the other hand, in diabetes mellitus there is a reduced capacity to utilize sugar and the arteriovenous blood sugar difference is less than normal. As a result less sugar is taken up by the tissues. After a carbohydrate meal the respiratory quotient remains low, and the fall in the level of inorganic phosphates of the blood following an increased supply of carbohydrates is less than normal. When the two diseases coëxist the diagnosis of diabetes mellitus is usually made first. Certain features during the course of the illness should arouse the suspicion that disease of the thyroid gland may be a complicating factor. Inability to control the glycosuria and the hyperglycemia with regulation of the diet and with what should be an adequate dosage of insulin are significant findings. Acidosis is prone to develop in these patients, especially if they are losing weight or are undernourished. Rapid pulse, restlessness, flushing, moist skin and tremor of the hands all aid in making the diagnosis of hyperthyroidism particularly in younger patients.

Cuttle[4] pointed out that diabetes mellitus in the young differs from the disease in the adult. The onset is abrupt and violent. The disease is more severe than in adults. It is usually progressive and it is more labile than in adults. There is a more definite relationship between juvenile diabetes and hyperfunction of the anterior lobe of the

hypophysis than is the case in adults. The condition is not usually preceded by obesity or by degenerative changes. In planning the treatment of diabetes these peculiarities should be taken into consideration. There should be adequate nourishment. A level of blood sugar below 200 mg. per 100 cc. should be established. There should be less than 10 gm. of dextrose in the urine in 24 hours. The cholesterol content of the blood should be below 230 mg. per 100 cc. There should be normal psychological adjustment and development. The psychologic adjustment of the child to the limits imposed by the disease may present a difficult problem. He must be taught the nature of his disease, its dangers and his part in the control, while at the same time he is educated to live happily with his disease.

White[30a] stated that in general the apparent difficulty in the management of juvenile diabetes has two explanations. The disease is uncommon in childhood. Therefore, unless the physician is especially interested in diabetes he sees few children afflicted with it and consequently he lacks experience. Then also since the commonest age of onset of diabetes is that of 12 years, the child is rarely treated by the pediatrician, whose mind should be unbiased, but more often by the general practitioner or physician who is accustomed to deal with diabetic adults and expects to find the same mental attitude in the young patient and applies the same standards for control and the same principle of treatment. Even the type of onset is characteristic, for in the child the disease is acute and virulent. Often the first recognition is made in the chemical coma, and the younger the patient the more striking is this fact. In the George F. Baker clinic the caloric requirement is based on surface area. Since in childhood this follows age closely, calories may be prescribed accordingly—1000 calories to an infant of 1 year with 100 calories added for each year of life. For girls a maximum of 2200 calories is reached at the age of 13 years. As soon as possible after maturity, the calorie prescription for girls should be reduced to avoid the obesity common in female adolescents. The maximum caloric diet prescribed for boys is 2800, a point reached at the age of 19 years. The ratio of carbohydrate to fat is selected according to one of two methods. Those who believe that stimulation of the pancreas results in improvement of diabetes prescribe carbohydrate-rich and fat-poor diets. Those who believe that rest of the pancreas is beneficial, prescribe low carbohydrate diets. All diabetic children require insulin and should be given it from the day that the disease is recognized and preferably continuously. After 3 years' experience with protamine insulin it is believed that this is the ideal form to use in the treatment of juvenile diabetes. However, unlike adults of whom 50% require no regular insulin in addition to the protamine insulin, it is found that 90% of children will require both regular insulin and protamine insulin. These should be given in separate injections simultaneously before breakfast.

Using a constant regimen of treatment for a selected group of children with diabetes mellitus, Jackson, Boyd and Smith[13] continued detailed hospital control until stability of insulin requirement and normal range of fluctuation in blood sugar have been attained. The regimen employed has been based on the premise that physiologic levels of control such as normal blood sugar levels, freedom from glycosuria or insulin

shock and complete adequacy of diet are desirable and attainable. They found that with strict hospital and laboratory control, a period of 6 weeks to 2 months was necessary to attain suitable stability of the sugar-handling function. Adequately prolonged hospital control of the patient at the outset of his management increased his subsequent stability under home management and avoided the difficulties which characterize the treatment of the diabetic child. With the establishment of such stability the insulin requirement became much smaller than during periods characterized by mild glycosuria or hyperglycemia. In view of this spontaneous lessening of the insulin requirement many studies that are reported as to the relative value of different types of insulin are open to question as to the conclusions that are drawn. Probably few children with diabetes mellitus in the country at large attain a desirable level of control, especially when preliminary stabilization is not complete and mild glycosuria is so frequently allowed. With improvement of level of control the authors predicted that there would be a lessening of complications, sequelæ and fatalities.

Herron[11] found that in managing diabetes in children one must take into consideration the growth and education of the child as well as the severity, instability and progression of the disease. The ideal was to produce a normal blood sugar throughout the 24 hours without shock or glycosuria and to produce normal growth and allow a happy existence. Individualization of dosage was necessary and was based on frequent determinations of the blood sugar and urinalyses. Hospitalization was recommended for new patients until the proper routine was established. Juvenile patients responded to protamine zinc insulin unusually well. It was found that a diabetic child cannot have a normal diet without insulin and he will not adhere to an inadequate diet. Most children do best on a high carbohydrate-low fat diet, because of the better metabolic balance. They show less tendency to go from hypoglycemia to hyperglycemia, a lowering of the insulin requirements in many cases, better adherence to the diet, an increase in carbohydrate tolerance and an increase in weight, strength and energy. A weighed diet was urged for the best control of the disease. Proper control allows normal growth and development and a happy existence.

Möllerström[19] expounded his ideas concerning the selection of food for diabetic patients, based on an experience with over 1000 cases. Illustrating the extremes to which non-physiologic thinking has led some authorities he pointed out Lundberg's advocacy of large amounts of vegetables and alcohol for the treatment of the acidosis in adults. Certain deficiency syndromes result from the fantastically one-sided diets that have enjoyed popularity. The pediatrician first introduced more physiologic diets. The need of an ample amount of carbohydrate is important. Since it seems that ketosis can follow from the incomplete conversion of carbohydrate to fat as well as from B-oxidation of fat, excess of carbohydrate may be harmful. It must be borne in mind that hyperalimentation is harmful, but starvation may precipitate grave dangers. Of these ketosis is the chief hazard. The metabolic consequences of hyperglycemia and glycosuria without acidosis are questionable. Although it is usually assumed that the atherosclerosis which so frequently accompanies diabetes in elderly people is a consequence of diabetes, it is also likely that the mildly diabetic state repre-

sents a defense mechanism to supply more dextrose to the undernourished myocardium. Although this may seem a novel concept it is supported by clinical evidence. The result may be that zealous treatment of the diabetic symptoms may exaggerate the myocardial inadequacy. As a general thing the effect of a given amount of insulin is significantly increased when its administration is timed in relation to the patient's endogenous rhythm. This rhythm is more clearly followed by studies of the diurnal fluctuations of acid formation than by studies of the urinary and blood sugar. The patient's own appetite should be one index of his requirements and should not be disregarded by prescribing a rigid, unvarying fare. There should be essential difference between the diet suitable for the child and for the adult diabetic.

Nelson and Ward[20] reminded us that prior to the introduction of insulin diet was the sole factor in the treatment of diabetes mellitus. The principle of treatment in the later portion of the pre-insulin period was induction of marked malnutrition and employment of diets high in fat and low in carbohydrate. Since 1922 there has been trend towards the use of normal or average diets. The aim of treatment of diabetic children has changed from mere prolongation of life to maintenance of adequate growth and normal activity. Although there have been distinct differences of opinion regarding the qualitative and quantitative content of the diet, the tendency has been towards a more liberal allowance of carbohydrate. The types of diets generally used include low carbohydrate and high fat; moderate carbohydrate and high fat; moderate carbohydrate and moderate fat; high carbohydrate and low fat; high carbohydrate and moderate fat; limited carbohydrate with other portions unlimited, and an entirely unrestricted diet. These groups overlap. Numerous advantages are claimed for the higher carbohydrate diets. Among these are the lower cost, its greater palatability and especially its approximation to the average diet so that all the members of the family may partake of it. This last point is an important one in the treatment of children. The actual efficiency of the diet is often measured in terms of the units of insulin required to balance it. The authors did not advocate the use of free and unrestricted diets, but felt that a more normal type of diet may be used than is sometimes advised. In favor of the use of measured diets the most important factor is the control of weight while others are the assurance of a balanced intake, instruction of the child by experience with the content of an adequate diet, reasonable distribution of the diet through the day and the psychologic effect of aiding the training of the child in self-discipline. This last factor is important but it is effective only so long as the child is given an ample diet. Diabetic children cannot be expected to adhere to inadequate diets.

Lichenstein[15] pointed out that those with experience in pre-insulin days remember the terrible existence that diabetic children had to sustain. The extremely strict diet supplied to these unfortunate children scarcely contained anything that could appeal to the taste of children in general. In spite of all privation the result of the strict diet always became unfavorable after a very short while. With the introduction of insulin new therapeutic prospects were opened. The new remedy gave the possibility of supplying a more liberal diet as well as

of meeting the risks of infection with more confidence and of overcoming the state of coma in a new way. It would have been possible earlier to have taken full advantage of the introduction of insulin. At first it was used as an auxiliary to a strict dietetic treatment, which was regarded as the main point. It still is regarded as the main point by many. The children still have to endure a restricted existence. They have not been allowed to enjoy the pleasure of satisfying their hunger in a normal way and they have still been treated as exceptions, which has been anything but advantageous especially as regards their psychical development. By degrees the views on this matter have changed. More and more the conclusion has been reached that children suffering from diabetes should be allowed to lead as normal existence as possible. The author has been using the free diet for several years and he has emphasized in his teaching the importance of letting the diabetic child have a chance of living a normal life with free choice of food buffered by a sufficient dosage of insulin. He defined free diet as an absolutely free diet without any restrictions and without weighing the food or any of its ingredients. In other words, the children are allowed to satisfy their appetite and to some extent their individual taste. The only restriction is the avoidance of luxury, which also ought to be avoided by normal children. The insulin is given in doses sufficient to keep the child in good general condition, in good increase of weight and free from ketone bodies in the urine. There is little importance to be attached to a somewhat greater or lesser sugar excretion provided the increase has not appeared in connection with a change for the worse in the general condition of the child or in the weight curve. The change from the restricted to the free diet has always been an easy one. The patients themselves and their families appreciate the release from strict dietary schedules and from the daily trouble of weighing and measuring the allowed quantity of food. There is a great joy on the part of the diabetic child at the release from the strict dietary regimen and when this has been seen it is possible to appreciate the altered psychologic condition from being placed in a method of living similar to that of normal children. This gives a favorable influence on the disease.

It was found that as a first result of the change the children showed a voracious appetite for carbohydrates. Very soon the child passed on to a more normal consumption of carbohydrates which varied but little. The supply of carbohydrates remained on a higher level than previously. Any inconvenience on account of the increased supply of carbohydrates was not observed. On the contrary, the condition of the patient was always influenced favorably by the change and often to a great extent. Even the weight curves manifested improvement, depending on the fact that not only the supply of carbohydrates but also the total supply of calories increased. It might be expected the blood sugar level, as well as the carbohydrate excretion, would be increased if the insulin dosage was not raised correspondingly. This was not the case. Although some patients on free diet have required larger doses of insulin than previously, the increase has usually been moderate and sometimes insignificant. In many cases the dose of insulin was maintained unchanged without inconvenience, and in some cases it was possible to reduce it, in spite of the fact that the supply

of carbohydrates was twice the amount previously given. The blood sugar level often proved to be more regular than before, sometimes a little higher, but sometimes considerably lower, and at the same time more uniform. The urinary sugar excretion has not been considerably higher during the free diet, but sometimes remarkably low in proportion to the large supply of carbohydrates. One inconvenience attached to the free diet was that when using regular insulin three injections must be given in 24 hours. However, when protamine insulin was used instead of the regular insulin it was possible to reduce the dose to even one per day in spite of keeping the child on the free diet. On free diet the danger of overdosage of insulin with its consequent trouble was far less. Another interesting fact was that the ketonuria disappeared or decreased considerably after the change to the free diet. This meant that the danger of coma was reduced. Because of this as well as because of the other advantages the return of the patients for hospitalization was avoided.

Feinblatt[6] made a comparative study of standard insulin, crystalline insulin, protamine insulin and hexamine insulin. He found that low blood sugars were maintained several hours longer on the crystalline insulin than on standard insulin. The unit value of protamine insulin was found to be greater and more lasting than the unit value of standard insulin. Another favorable finding was that under this form of insulin there was an absence of ketonuria and decreased incidence of lipemia. The introduction of protamine insulin was a great advance in the treatment of diabetes as the practicality of a single daily injection encouraged both the patient and the physician to favor insulin therapy. A later modification was hexamine insulin. This is a compound of insulin and hexamethylene tetramine. This form is also used in a single dose. In this study it was shown that the blood sugar curve could be kept at a lower level than with protamine insulin and with smaller fluctuations during the day. There was also the striking absence of ketonuria. This insulin was also found to have the specific effect in decreasing polyuria in those patients who complained of it under standard insulin and under protamine insulin.

Alpert[1] offered a new therapy by combining protamine insulin and hexamine insulin. He stated that when these were mixed in the same vial they retained their individual characteristics as is evidenced by the blood sugar time curves. The hexamine insulin gave an immediate as well as some intermediate blood sugar lowering effect, while the delayed action of the protamine insulin was preserved. The use of the combined hexamine and protamine insulins eliminated the necessity for supplementary injections of insulin during the day. In the mixture of these two insulins the hexamine insulin remains fluid while the protamine remains a precipitate.

The most frequent complication of diabetes is tuberculosis. Nobecourt, Ducas and Scheinmann[21] pointed out that among adults it has been found to be the chief cause of death since the introduction of insulin has reduced deaths from distinctly diabetic causes. Before the use of insulin the short course of diabetes in children, which averaged about $2\frac{1}{2}$ years, prevented the evolution of coincident tuberculosis, but since the introduction of insulin this complication has been found in many juvenile diabetics. When a diabetic child becomes tuberculous it is

of interest to observe the influence of the tuberculosis on diabetes and the influence of the diabetes on tuberculosis. As regards the influence of tuberculosis on diabetes, it has been recognized that in the adult tuberculosis aggravates the disequilibrium of the glucosides, favors the onset of acidosis and establishes a relative resistance to insulin. In the child the effect was found to be similar but much less marked. A rigid dietetic regimen was recommended to avoid disaster. The rôle of diabetes in the evolution of tuberculosis depended on the therapy that was instituted. Sometimes diabetes preceded the appearance of tuberlosis. They believed that in diabetic children tuberculosis had an acute onset.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MAY 10, 1941

Synthesis of an Isomer of Corticosterone. MAXIMILIAN EHRENSTEIN (Cox Institute, University of Pennsylvania). Recent evidence points to certain physiologic differences between desoxycorticosterone and corticosterone. Both substances occur in adrenal-cortical extracts. At present only desoxycorticosterone has been obtained by synthesis. Corticosterone differs from desoxycorticosterone in that it has a secondary hydroxyl group attached to carbon atom 11. The synthesis of

corticosterone itself appears extremely difficult. We were successful, however, in synthesizing the acetate of an isomer of corticosterone which has one hydroxyl group attached to carbon atom 6 instead of carbon atom 11. It remains to be seen how far the physiologic action of this substance differs from that of corticosterone and desoxycorticosterone.

21-Acetoxy-pregnenonol which can be synthesized from cholesterol served as starting material for this investigation. By treating it with perbenzoic acid a mixture of (5:6)-oxides was obtained which contained mainly the α configuration [Pregnane-(5:6) (α)-oxide-20-1-3.21-diol 21-monoacetate]. The oxide ring of this substance was ruptured by means of glacial acetic acid with the formation of a 6-acetoxy-compound. [Pregnane-20-1-3.5. 6.21-tetraol 6.21-diacetate.] To a minor extent acetylation took place also at carbon atom 3. The main product of the reaction was subjected to an oxidation with chromic acid which furnished Pregnane-3.20-dione-5. 6.21-triol 6.21-diacetate. Dehydration of the latter substance by means of dry HCl gas in a solution of chloroform yielded the diacetate of 6-Hydroxy-Desoxycorticosterone

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Apparatus for Recording Cyclical Activity in the Rat and Correlation of Leukocyte Count With Peak of Estrus.* Edmond J. Farris (The Wistar Institute of Anatomy and Biology). A new apparatus was designed to register the number of revolutions of a turntable per unit of time. The revolutions of turntables in rat cages are registered on magnetic counters mounted on a panel in another room. The counters are photographed on the hour for continuous 24- or 48-hour records, by time-lapse mechanism. The apparatus is accurate for determining peak, regularity and length of estrus cycle. The system of cages and apparatus is arranged to reduce handling of animals to a minimum, and consequently neurophysiologic (emotional) stimulation is practically eliminated, for the animals are handled only once a week.

It was found that with peak of activity there was a leukopenia and during the diestrus interval, a leukocytosis. Constant darkness activity records were discussed.

Motion Picture Showing Chemotaxis of Leukocytes. D. R. Coman (Department of Pathology, University of Pennsylvania). A moving picture of rabbit polymorphonuclear leukocytes, showed the chemotactic responses of these cells to various substances. Positive chemotaxis to collodion, negative chemotaxis to a silicate and random motion (indifferent chemotaxis) to carbon, were shown.

The Quantitative Measurement of Cerebral Blood Flow in the Monkey. C. F. Schmidt and P. R. Dumke (Department of Pharmacology, University of Pennsylvania). Quantitative measurements of

* This investigation was aided by a grant from the Samuel S. Fels Fund.

cerebral blood flow have been frustrated hitherto by anatomic difficulties (abundant and inaccessible communications between the intracranial and extracranial parts of the cephalic circulation, particularly in the dog and cat) as well as by shortcomings in the various methods that have been used for this purpose (stromuhr, venturimeter, diversion of venous outflow into a calibrated vessel, thermocouple in brain tissue or in a vein effluent from the brain, thermostromuhr, rotameter). In the present experiments both of these objections have been met, the anatomic by the use of an animal (*Macacus rhesus*) in which blood carried by the internal carotids is distributed only to the brain and is the sole supply of that organ if the basilar artery is tied, the instrumental by timing the transit, through a glass tube of known volume, of an air bubble injected into the stream of blood carried from the common to the internal carotid arteries, the animal being narcotized with nembutal and heparinized and its basilar artery ligated.

In 14 experiments cerebral blood flow thus measured at the start of the experiment ranged from 0.38 to 0.81 and averaged 0.62 cc. per gram of brain per minute. Flow was consistently increased by intracarotid injections of non-depressor doses of histamine, nitroglycerin, theophylline and caffeine, as well as by inhalation of CO_2 (10%) in oxygen or of pure nitrogen; the effect of histamine was much greater and that of CO_2 much smaller than was expected from results of experiments on cats. Small doses of adrenalin and benzedrine intra-arterially consistently caused a significant decrease in cerebral blood flow sufficient in some instances to cause symptoms of cerebral anemia; with intravenous injections an increase in flow preceded the decrease and the latter was less striking though usually present. Ergotamine diminished cerebral flow consistently, but it also lowered blood pressure. Stimulation of the cervical sympathetic nerve did not decrease the flow in any of 9 attempts on 4 animals though typical ocular effects were observed. Metrazol, in convulsant doses, caused a pure increase in the flow. With insulin, blood pressure fell as hypoglycemia developed and then recovered; cerebral flow followed this, apparently quite passively. Further experiments are being made.

The Circulation in Traumatic Shock. MILTON L. CULLEN, A. E. SCHECTER, NORMAN E. FREEMAN, and M. K. LAWS (Harrison Department of Surgical Research, Schools of Medicine, University of Pennsylvania). Shock was produced by trauma to the muscles of both thighs in 9 of 11 intact dogs and in 5 partially sympathectomized dogs. Local fluid loss was excessive in all instances. The earliest sign of shock was a marked reduction of peripheral blood flow as measured in the dog's uninjured paw. Hemoconcentration was not a significant finding. Shock was produced in 14 of 16 dogs by muscle trauma combined with fractures of two ipsolateral extremities but the local fluid loss was restricted by binding the extremities with tape. The amount of fluid lost into the injured extremities was measured. The earliest sign of shock was a marked reduction of peripheral blood flow. There was considerable hemoconcentration in comparison to the earlier experiments.

Blood volume determinations by the carbon monoxide method showed a substantial reduction of blood volume after trauma, and this reduction was only partially accounted for by local fluid loss.

Postmortem examinations suggest that at least part of the "lost" blood volume is to be found in the lumen and wall of the intestinal tract.

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